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This population-based study examines early life exposure to environmental pollutants from industrial sites, toxic waste sites and heavily trafficked roadways as risk factors for breast cancer; with a focus on exposure to benzene and PAHs. We have geocoded 15,340 individual addresses for 3,286 participants in Erie and Niagara counties in the study. A validation study assessed the positional accuracy of addresses geocoded on the Dynamap2000 using a global positioning system receiver. Overall, geocoding was accurate. Analyses have been completed examining residential proximity to industrial sites contracting with the US Atomic Energy Commission (USAEC), for exposure to total suspended particulates (TSP), and exposure to environmental tobacco smoke (ETS) and breast cancer risk. Proximity to sites contracted by USAEC was not associated with risk. Exposure to TSP in early life was associated with a 2.75-fold increase in risk for postmenopausal women only. There was little evidence of an association between early life exposure to ETS and breast cancer. Clustering analyses identified geographic patterns of residence for breast cancer cases and controls at critical time periods in early life. These results provide evidence that environmental exposures in early life may be important for breast cancer risk.

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INTRODUCTION

In this population-based study we are examining environmental exposures experienced at birth and at menarche as risk factors for breast cancer. We are in the process of examining location of residence during these potentially sensitive time periods in relation to proximity to industrial sites, gasoline stations, toxic waste sites and heavily trafficked roadways as risk factors for subsequent disease. Residential histories were obtained from all participants during our case-control study, which ended May, 2001. This study included women, age 35-79 with incident, primary, histologically confirmed breast cancer living in Erie or Niagara counties. Controls are frequency matched to cases on age, race and county of residence. Residence at the time of birth and menarche, as well as the potential exposure sites will be geocoded into GIS. The primary objectives of this study are: 1) To investigate distance from steel mills, chemical factories, gasoline stations, toxic waste sites, other industrial sites and major roadways of the residence of cases and controls at the time of birth and at menarche as risk factors for pre- and postmenopausal breast cancer. 2) To examine estimated exposure to benzene and to PAHs as risk factors for pre- and postmenopausal breast cancer. 3) To evaluate genetic susceptibility in relation to these exposures and breast cancer risk by examining genetic variability in metabolism by NQ01, GST M1-1, GST P1-1 and CYP 1A1. Potential confounding factors will also be assessed. These include age, education, income, family history of breast cancer, Quetelet index, body fat distribution, having been breastfed, age at menarche, age at menopause, pregnancy history, lactation and contraceptive history, menstrual cycle length, birth weight, smoking and passive smoke exposure history, and diet and occupational history. Results to date are discussed in the text of this report.

BODY OF REPORT

Task 1: Investigate distance from steel mills, chemical factories, gasoline stations, toxic waste sites, and other industrial site of the residence of cases and controls at the time of birth and at menarche as risk factors for pre- and postmenopausal breast cancer.

Task 1 is completed. We have identified and completed data entry for relevant industrial sites and major roadways during time periods under investigation. We have identified additional sources of information regarding historical sources of the exposures of interest and their locations and amounts. We have verified and geocoded residential histories of study participants. We have completed the geocoding for study participants for their residence at the time of their birth, at menarche, when they had a first birth and 10 and 20 years before diagnosis (cases) or interview (controls). In total, we have geocoded approximately 20,000 addresses in Erie and Niagara counties. In addition, we have conducted a validation study of the positional accuracy of geocoded residences. Results of this validation study will be published in the journal Epidemiology in July 2003. We have also completed data analysis examining early life proximity to industrial sites contracted by the United States Atomic Energy Commission in relation to risk of breast cancer in adult life. Currently a manuscript for these analyses is in preparation and will be submitted for publication in the next several months.

Two abstracts from the work on this task were presented at the annual meeting of the Society for Epidemiologic Research in Atlanta, Georgia, June 11-14, 2003 and the abstracts will be published in a supplement of the American Journal of Epidemiology. They are: "Residential Proximity to Chemical or Primary Metal Industry and the Risk of Breast Cancer in Western New York," and "Clustering of Lifetime Residence and Breast Cancer Risk in Western New York." Copies of the abstracts are in Reportable Outcome Section.

We completed a GIS-based spatial and temporal analyses for residences of breast cancer cases and controls at early life. Since we found strong evidence of spatial clustering for cases at early time periods, we will continue with the next step which is to estimate breast cancer risk associated with environmental exposures at those early residences. Epidemiologic investigations on the evaluation of environmental risk factors and the estimation of breast cancer risk associated with lifetime residential history will be performed with the aid of GIS and spatial perspectives. Manuscripts are in preparation regarding the clustering of residence in early life that we found. Descriptions of findings follow.

A. Analysis of Geographic Clustering of Cases and Controls by Period of the Lifetime

1. Spatial clustering of residences associated with early life event

We examined the geographic location of breast cancer cases and controls at places of residence associated with three early life events - residence at birth, menarche, and

women's first birth - to identify spatial patterns of clustering. The *k*-function provides an effective summary of the underlying nature of point patterns, whether clustered or dispersed. The essential question is whether cases are more clustered than the underlying population, as represented by the controls. We obtained differences between the two point patterns for locations associated with each early life event by calculating all inter-point distances of cases and controls. Figure 1 illustrates the *k*-function differences for values of *h* up to 15 miles, together with the approximate 95 % confidence envelopes. The value of *h* is generally taken as one-third of the linear extent of the study area (Rowlingson and Diggle, 1993). Any patterns beyond this scale can be disregarded, since either peaks or troughs in this geographic scale are difficult to interpret, and are potentially misleading.

Figure 1a shows the *k*-function differences at birth residence. It is clear that the estimated function shows strong evidence of spatial clustering, that is, of clustering of cases relative to controls at the scale of about 3-15 miles. There was no significant difference up to 3 miles, while statistically significant differences were detected beyond the scale of 3 miles. There is also evidence of some degree of clustering for breast cancer cases at menarche residence (Figure 1b). While estimates of the *D*-function are positive but not statistically significant up to 7 miles, it is evident that spatial clustering of breast cancer cases occurs at a scale of about 7-15 miles. For residence at women's first birth, the difference is not statistically significant because the plot falls within the confidence interval over all distances. In summary, while there is clear evidence of clustering of breast cancer cases with respect to controls at time of birth and menarche, there is no clustering at the time of first birth residence. It is interesting that we found evidence of spatial clustering of breast cancer cases at residence of early events while there is no evidence of clustering for current addresses (see Figure 1d).

Furthermore, the *k*-function difference was performed for pre- and post-menopausal women separately to determine whether there are any differences in clustering patterns by menopausal status. Results of the clustering analysis are shown in Figure 2. Graphs portraying the *k*-function differences between pre-menopausal breast cancer cases and controls and post-menopausal cases and controls were obtained for birth and menarche residences only, based on the evidence of spatial clustering in the above. It is interesting to find the same results for both early life events; we found very significant clustering of pre-menopausal breast cancer cases compared to controls for both birth and menarche residence (Figures 2a and 2b). Estimated functions at birth residence show a strong clustering of pre-menopausal cases over the entire geographic scale with a peak at 7 miles, while values are positive for post-menopausal cases, but not statistically significant. For menarche residence, we also observed a strong clustering of pre-menopausal cases with a peak at about 8-10 miles. Differences are not statistically significant for post-menopausal women at menarche residence. Since patterns of post-menopausal women show no differences between cases and controls for both birth and menarche residence, we may conclude that spatial clustering associated with place of residence at these two early life events is mainly attributable to the clustering cases among pre-menopausal women. While it is not clear what has driven the spatial clustering of pre-menopausal women for both birth and menarche residence, further epidemiologic investigation is required to provide explanations of this difference.

Finally, we examined breast cancer risk associated with residence in the cluster at the time of birth and menarche. The underlying assumption of this analysis is that there is a higher likelihood of getting environmental exposures, and thus higher breast cancer risk for subjects living in the cluster at the time of birth or menarche than subjects living in the rest of the study area. We first identified clustering of birth residence for pre-menopausal cases compared to pre-menopausal controls. A breast cancer cluster, an area with higher intensities for pre-menopausal cases, was detected with 5.7 mile radius in the areas near the city of Buffalo, and towns of Amherst, Cheektowaga, Tonawanda. The cluster is significant at <0.01 with 999 Monte Carlo simulations. We observed an elevated breast cancer risk for pre-menopausal women living in the cluster at the time of birth (Table 1). With subjects living in the outside of the cluster as a reference group, we obtained a crude odds ratio of 2.62 with 95% confidence interval of 1.76 and 3.91. The adjusted odds ratio 2.65 was also obtained after controlling for age, education, age at menarche, parity, history of benign breast disease, and family history. We also identified clustering of menarche residence for pre-menopausal women and obtained similar results as the results from birth residence. We identified a small clustering of menarche residences for pre-menopausal women. However, it is a small-sized cluster with 0.8 mile radius and there are only nine cases inside the cluster. A secondary cluster was also detected near the city of Buffalo with a three mile radius, but it is not statistically significant.

Table 1. Breast cancer risk between pre-menopausal women living in the cluster and the rest of the study area at the time of birth

	Cases	Controls	Crude OR	Adjusted OR*	95% CI	*p*-value
The Rest	60	173	1.0	1.0		
Cluster	100	110	2.62	2.65	1.75-4.0	<.01
Total	160	283				

* Adjusted for age, education, age at menarche, parity, history of benign breast disease, and family history.

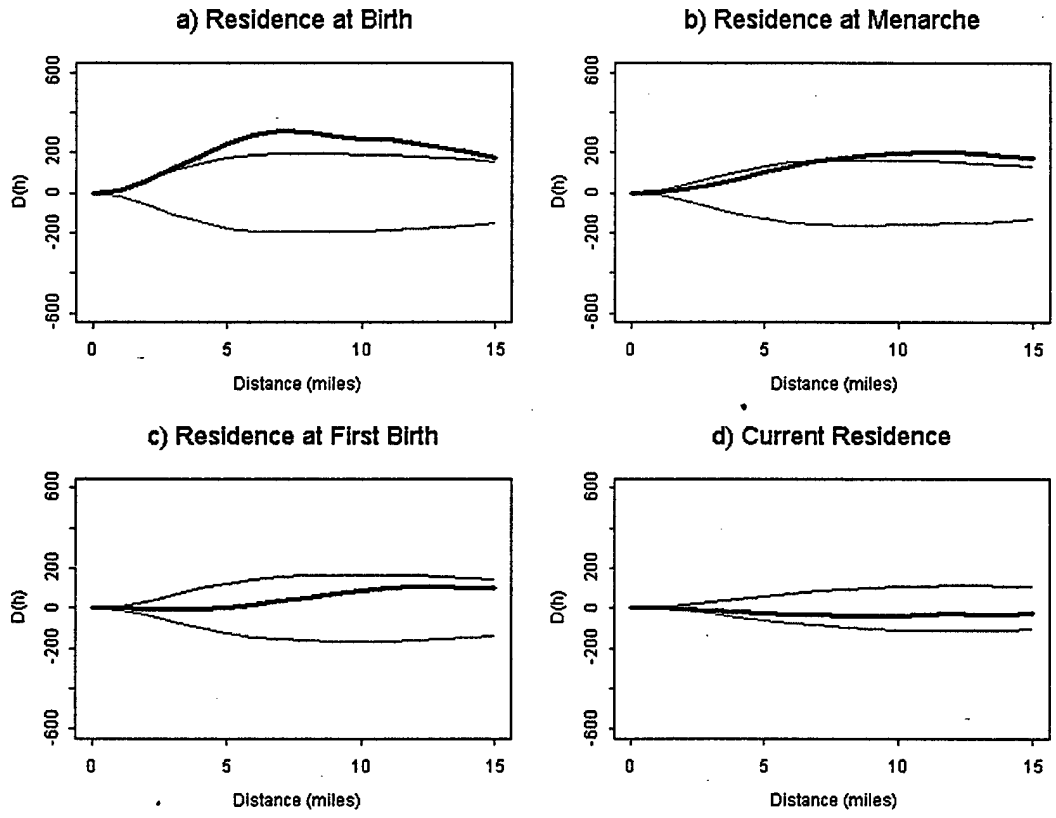


Figure 1. *k*-function differences in clustering patterns between cases and controls

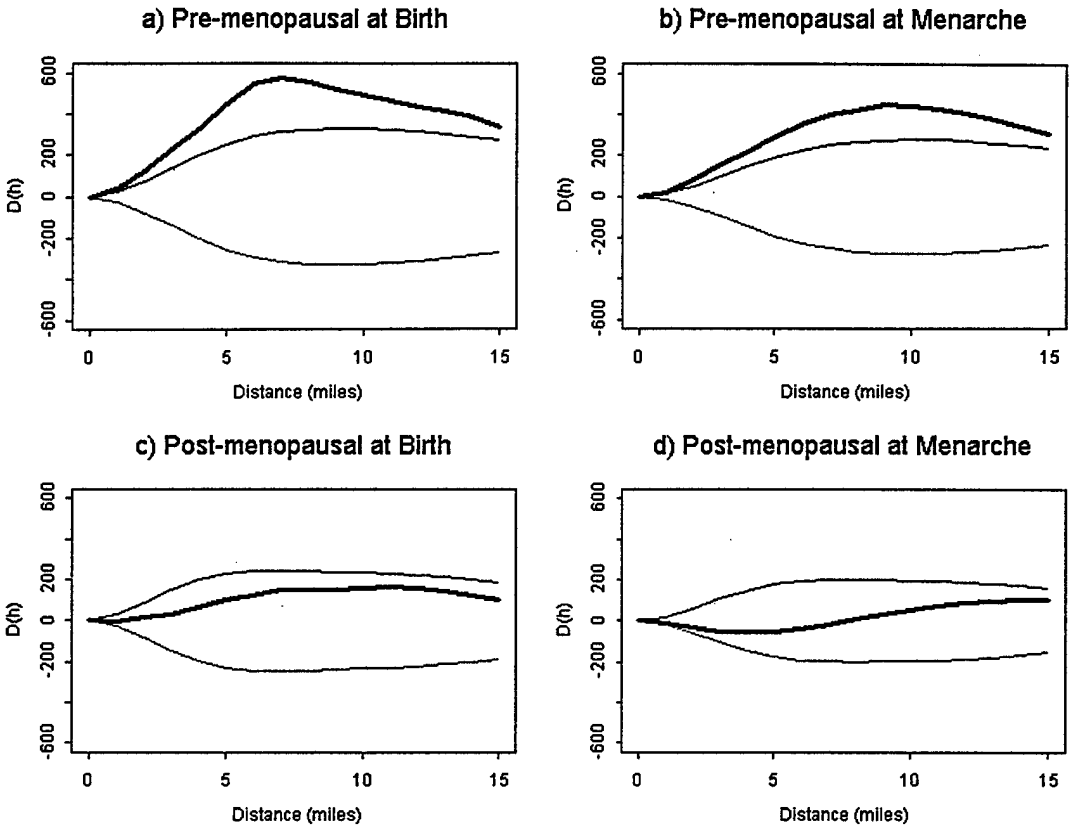


Figure 2. *k*-function differences between cases and controls by menopausal status

2. Identifying risk surfaces in space and time

We examined breast cancer risk associated with lifetime residential history to identify spatio-temporal patterns of risk surfaces in a population-based case-control study of breast cancer. With a growing interest in early or lifetime exposures to breast cancer risk, a life-course approach was adapted to see whether environments in early life or biological processes around critical events in a life-course may be related to disease in adulthood (Kuh and Ben-Shlomo, 1997; Barker, 1992). We explored the use of density estimation methods in epidemiologic studies as GIS-based exploratory spatial analyses, and obtained risk surfaces using several measures such as smoothed ratio and standardized difference. These risk surfaces were produced and compared between residences for pre-menopausal and post-menopausal women. It provides risk surfaces from lifetime residential history, thus more accurate estimates than density surfaces based on only current residential location.

We used six temporal groups, place of birth, the primary residence during the period of menarche, and the primary residence during women's first birth, residence 10 and 20 years prior to diagnosis for the cases and prior to interview for the controls, and current addresses. Geocoding of residential locations in six temporal groups are essential parts of this study which enables us to record each individual's locational information as x and y coordinates to be used in further spatial analyses. Overall address matching rates were 92.5%. Table 2 is a summary table showing the final numbers of cases and controls for those six events.

We first identified areas with higher than average densities of breast cancer cases in the study area based on the relative densities of cases to controls. Figure 3 shows the residential locations of breast cancer cases and controls in western New York. There are 4,808 residential locations for cases with 1334 pre-menopausal and 3470 post-menopausal residences, while there are 8,580 residential locations for controls with 2559 pre-menopausal and 6010 post-menopausal residences. We produced two maps of risk surface based on residential locations of cases and controls in Figure 3. Figure 4 shows risk surfaces of pre- and post-menopausal residences, and depict only areas of high case densities in the study area (ratio greater than 0.5). For instance, areas with ratio greater than 0.76 (with contours) indicate two times of increased breast cancer risk.

Second, standardized difference in case and control density is obtained to assess variability of risk surfaces. Figure 5a and 5b depict areas of greater than two standard deviations (with contours), and those statistically significant areas with images (over the critical value 3.5). There are several areas of interest for pre-menopausal residences; two in the center of the study area, and one in rural area, while only one in rural area was detected for post-menopausal residences. These are statistically significant areas exceeding the critical value at α=.01, indicating density of cases are significantly higher than that of controls. However, interpretation should be cautious on the ones appeared in rural area for both pre-menopausal and post-menopausal residences. As seen in Figure 3, there are very sparse residences in those areas. Although it is suggested that the

difference between case and control density is significantly different, it is not reliable because small sample size may influence on the results.

Finally, we were interested in finding time periods contributing to this result. Standardized difference is obtained for each temporal group, and pre- and post-menopausal residences separately. Figure 6 and 7 shows risk surfaces difference in space and time. As seen in Figures 6 and 7, areas greater than 2 S.D. are illustrated for each temporal group with darker images as statistically significant areas of high case density. Testing for significance are performed and attached as p-values. We found three time periods of interests; birth, menarche and 10 years for pre-menopausal residences. These areas are significantly different at $\alpha.=0.1$ and indicate areas of high case densities. For post-menopausal residences, we found one significant time period (20 years) at the .1 level. Once again ones in rural area for 10 years in Figure 6 and 20 years in Figure 7 seem to appear due to small sample size of the area.

Table 2. Residential history of breast cancer cases and controls

	A-Complete Addresses						B-Missing		C-Total (%A/C)
	Cases			Controls					
	Pre-	Post-	All	Pre-	Post-	All	Cases	Controls	
Birth	160	283	505	345	521	804	127	189	1642(80)
Menarche	204	386	673	469	757	1143	98	154	2068(88)
First birth	181	371	616	435	782	1153	97	167	2033(87)
20 years*	210	672	882	413	1201	1614	96	157	2749(91)
10 years*	258	717	975	501	1266	1767	74	133	2949(93)
Current	327	826	1157	619	1469	2099	12	18	3286(99)
Total	1334	3470	4808	2559	6010	8580	504	818	14727(91)

* 20 and 10 years prior to diagnosis or control selection respectively

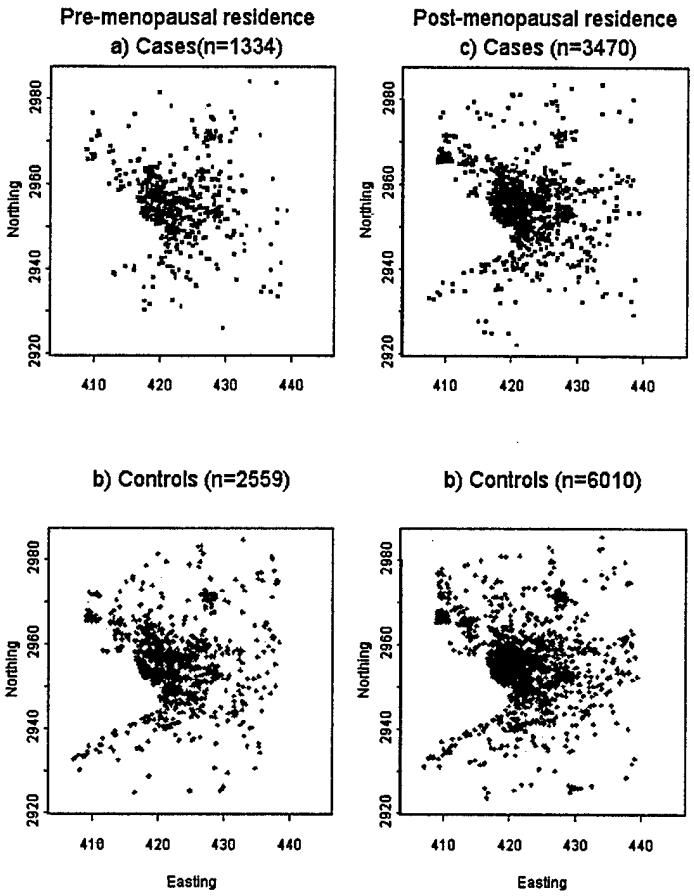


Figure 3. Geographic distribution of breast cancer cases in western New York: All residential locations of breast cancer cases and controls included in the analysis

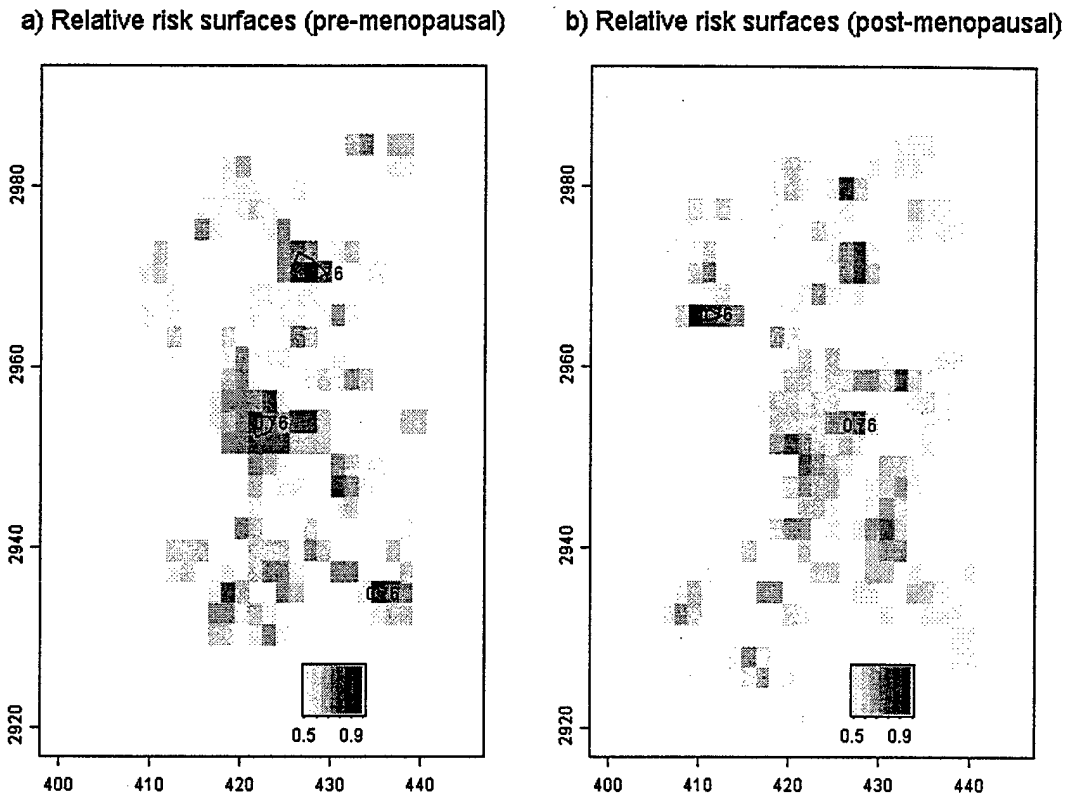


Figure 4. Risk surfaces for pre-menopausal and post-menopausal residence

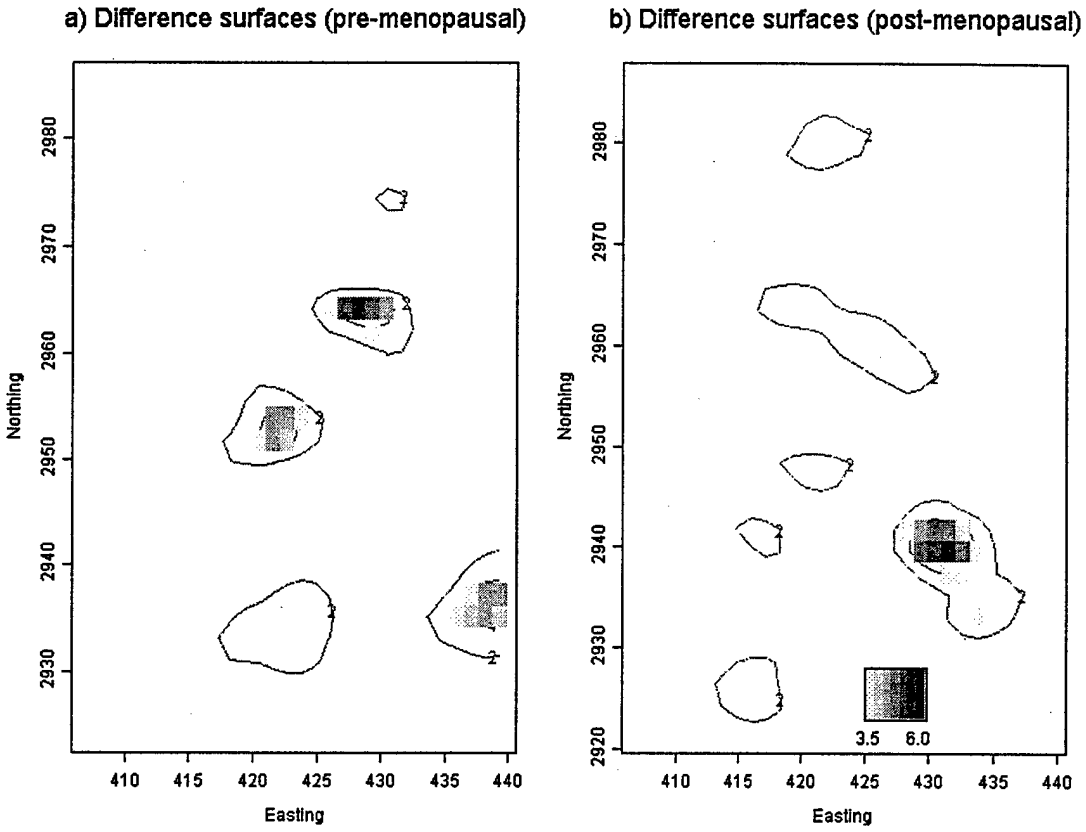


Figure 5. Difference in risk surfaces for pre-menopausal and post-menopausal residence

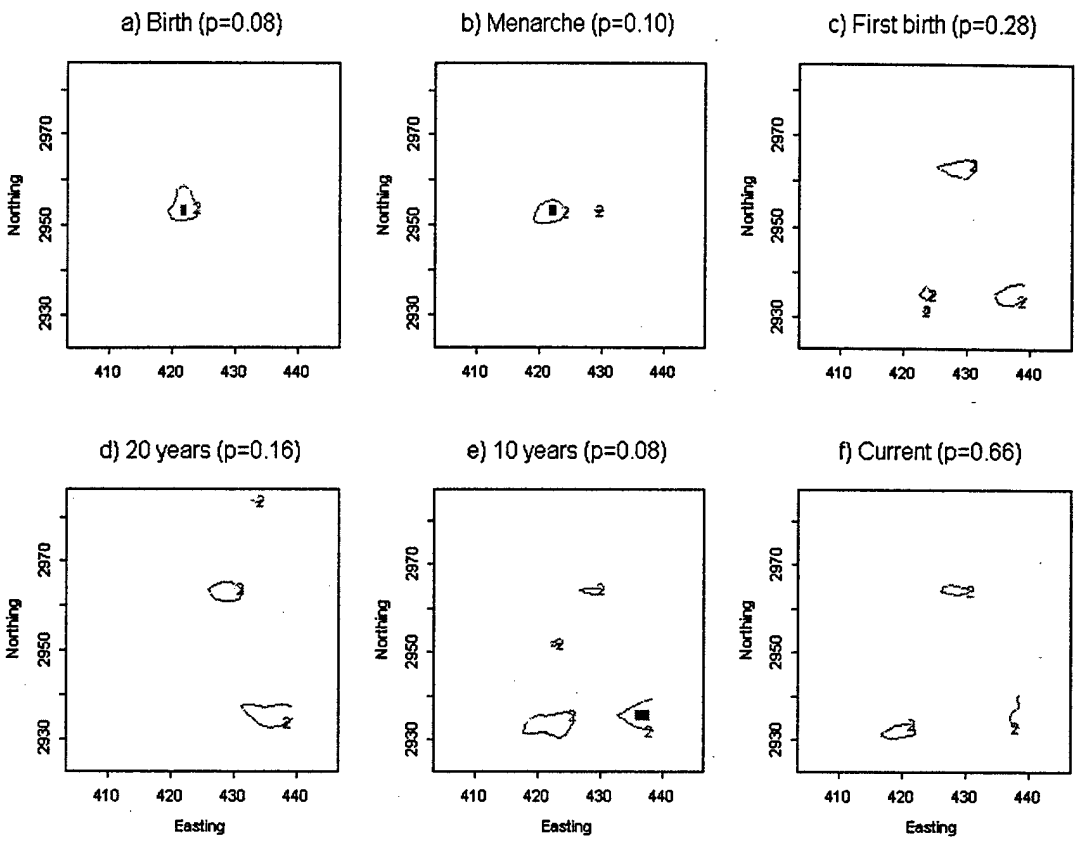


Figure 6. Risk surface difference in space and time: pre-menopausal residence

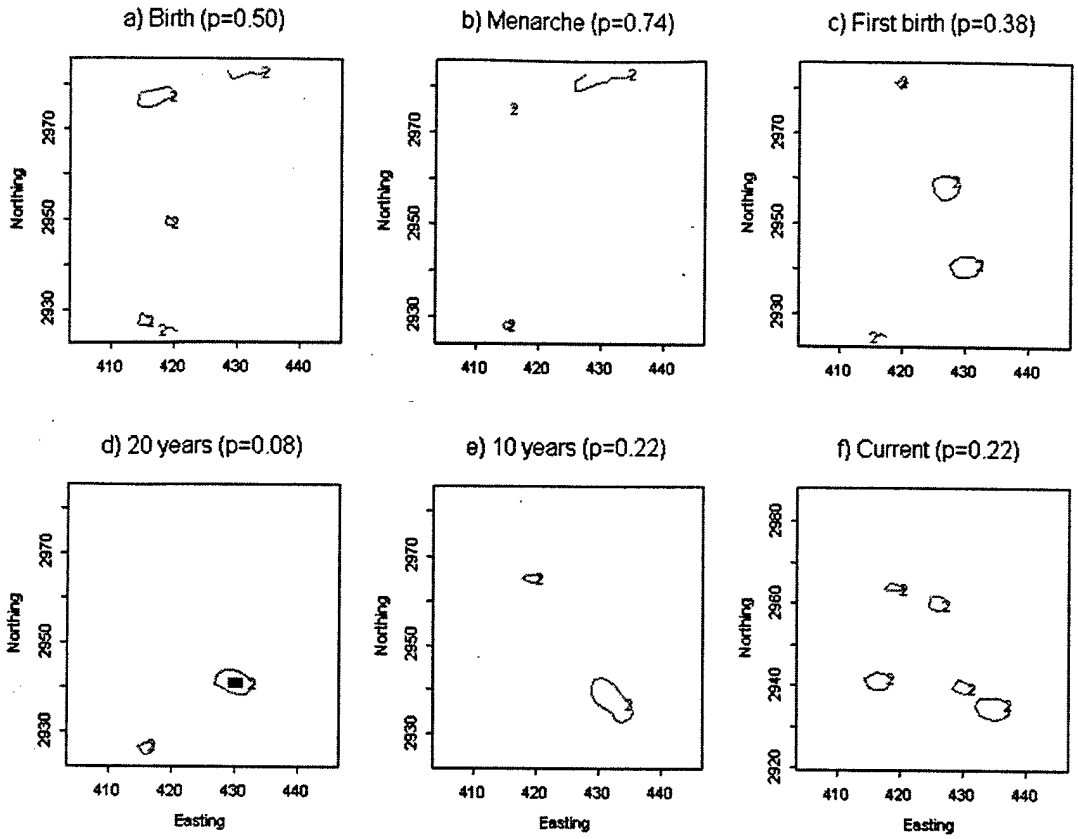


Figure 7. Risk surface difference in space and time: post-menopausal residence

B. Examination of Breast Cancer Risk in Relation to Residential Proximity to Industrial Sites Contracted by the U.S. Atomic Energy Commission.

Ionizing radiation is a well-recognized human mammary carcinogen. Numerous studies including those of Japanese atomic bomb survivors and tuberculosis patients treated with radiation have shown that breast epithelium is radiosensitive to external radiation.[1-7] In addition, exposure at early age appears to be particularly important. Less is known about the effects of internal radiation on breast epithelium. The epidemiologic evidence regarding internal emitters and breast cancer comes primarily from radium dial workers and from German patients treated with high doses of radium-224 for ankylosing spondylitis and tuberculosis.[8] In the German patients, adult women treated with radiun-224 had an SIR of 1.77 for breast cancer, while women < 21 years of age when treated with radium-224 had an SIR of 9.4, further suggesting that early life exposures may be important in mammary carcinogenesis, albeit at high doses. The effects of low-dose exposure to the general population, however, have not been demonstrated and are generally extrapolated from high-dose exposures.[9]

The general population is exposed to low-dose internal and external radiation from both natural and anthropogenic sources. Natural sources include decay of uranium present in soil, dissolved in water, and absorbed by plants and animals that are consumed. Man-made sources include therapeutic radioactive isotopes, consumer products such as tobacco and smoke detectors, the nuclear power industry, and the military nuclear industry.[10]

In the 1940's and 1950's, the United States Atomic Energy Commission (USAEC) and its predecessor the Manhattan Engineering Project (currently, the United States Department of Energy) contracted with numerous private industries to process uranium for the burgeoning nuclear program. In Erie and Niagara Counties in Western New York State, 13 such industrial sites contracted with the USAEC to enrich uranium, mill uranium metal, or to store radioactive waste. In addition to these USAEC activities, these sites were also engaged in commercial industrial activities such as steel and chemical manufacturing. In this case-control study we examined women's residential proximity to these sites at the time of their birth, at menarche, and when they had their first birth in relation to breast cancer in adult life. These industrial sites were examined because they were relatively close to residential neighborhoods and were engaged in processing radioactive material that resulted in residual environmental contamination at most sites. We have focused on early life exposure because it appears that it is the critical time period in breast development when breast epithelium is particularly sensitive to effects of ionizing radiation.

For this study, we postulated that women exposed in early life to radiation from uranium-238, uranium-235, radium-226 and thorium-232 from USAEC site activities would be more likely to develop breast cancer than women without these early life exposures. Specifically, we hypothesized that women born in close proximity to USAEC sites would be more likely to develop breast cancer than women born further away. In addition, we also predicted that women who resided in close proximity at the time of menarche and at first birth would also have increased odds of breast cancer compared to women residing further away from these sites at menarche and first birth.

Methods

A population-based, case-control study was conducted to evaluate the proposed hypotheses. Cases consisted of 1,166 women aged 35-79 living in Erie or Niagara County diagnosed with histologically confirmed, primary, incident breast cancer between the years 1996 and 2001. Controls under 65 years of age were randomly selected from the New York State Department of Motor Vehicles driver's license list and controls 65 and over were randomly selected from the Healthcare Financing Administration Medicare rolls. Controls ($n = 2,105$) were frequency matched to cases on age, race, and county of residence. The response rates for the cases were 59% and 35% for the controls. Refusal to participate was the he most common reason for both cases and controls. These estimates of response are somewhat conservative in that they include in the denominator 18% of cases and 45% of controls where eligibility could not be determined. With these individuals removed from the denominator, the response rates were 72% for cases and 79% for controls. The true response rate, however, most likely lie somewhere between these two estimates for cases and controls.

Extensive in-person interviews and self-administered questionnaires were used to ascertain medical history, diet, alcohol consumption, smoking history (including passive smoke exposure), residential history, and occupational history. Each participant listed all their residencies for their lifetime starting with the address at the time of interview. When a subject could not provide a complete address in Erie or Niagara County, Polk directory and city directory were searched to find this missing information. These histories were used to locate each subject's residence at birth, menarche, and first birth.

For the proximity at birth analyses, cases and controls were restricted to those with birth addresses in Erie or Niagara Counties. Of these, a further 241 cases and 380 controls were excluded from these analyses because they were born prior to the period of USAEC activities in this region (1942-1956). A total of 261 cases and 424 controls were included in the birth analyses.

For the analyses assessing exposure at menarche, cases and controls were restricted to those with an address in Erie or Niagara Counties at the time of menarche during the period of USAEC activities, leaving 581 cases and 918 controls. For the analyses assessing proximity at first birth, cases and controls were restricted to those with an address in Erie or Niagara Counties at the time of birth of their first child. Of these, one case and 14 controls were excluded because their first birth occurred prior to USAEC site activities for a total of 615 cases and 1,139 controls.

Exposure Assessment

Proximity to USAEC industrial sites was used as a surrogate for exposure to radioactive pollution emanating from these sites. Proximity to USAEC sites was calculated in a two step process. All birth, menarche, and first birth addresses were geocoded with ArcView 3.2 (ESRI, Inc., Redlands, CA) on the Dynamap2000 reference theme (Geographic Data Technologies, Inc., Lebanon, NH). The addresses of all 13 USAEC sites were also geocoded onto the same reference theme. An extension to ArcView 3.2 was used to calculate a distance matrix for each address to each of the 13 USAEC sites.

Subjects could theoretically be exposed to pollutants from all 13 sites; however, we used the closest site to calculate proximity with the rationale that the closest site would

contribute the majority of exposure. An algorithm was created in SAS (SAS Institute, Inc., Cary, NC) to determine the closest site dependent on the year that the subject's critical event occurred (i.e., birth, menarche, or first birth) and the years in which the USAEC sites were actively engaged in production or processing of radioactive material. This was done to ensure that only active plants were used to determine proximity. For example, there were only two plants operating in 1942. Consequently, for participants born in 1942, their closest site would be one of those two plants. We opted not to use those subjects born prior to USAEC activities as the truly unexposed because of the potential to introduce a birth cohort effect. Furthermore, there were only two premenopausal women who were born prior to 1942, precluding a comparison of this type for the premenopausal women.

Radiological surveys[11-21] for 9 of the 13 sites were obtained from the United States Army Corps of Engineers. Radiological surveys were conducted primarily by the National Laboratory at Oak Ridge to assess the amount of radiological contamination present on these sites for the Formerly Utilized Sites Remedial Action Program. These surveys were used to estimate the potential for off-site contamination and to estimate radiologic dose from that contamination. Whole body dose was estimated with the RESRAD 7.0 code (Argonne National Laboratory, Argonne, IL) using the default values and the average soil concentrations of uranium-238, uranium-235, radium-226, and thorium-232 at the Linde Ceramic Plant, which had the highest ground concentrations of uranium-238, uranium-235, radium-226, and thorium-232 of all the sites. Average soil concentrations of these radionuclides were derived from the radiological surveys. Radiological surveys for the remaining four sites either were never done or could not be located.

Statistical Analyses

The Student's *T*-test and Pearson's Chi-square test[22] were used to compare demographic and reproductive characteristics between cases and controls. The distance to the closest site was categorized into quartiles based on the distribution of distance in the controls. The closest quartile was further divided in two at the midpoint to provide higher resolution for the closest distances. Logistic regression[23] was used to calculate odds ratios (OR) and 95% confidence intervals (95% CI) for each quartile compared to the furthest quartile. Multiple logistic regression was used to assess potential confounding by age at interview, race, education, age at menarche, parity, age at first birth, previous benign breast disease, family history of breast cancer, body mass index (height (m)/weight $(kg)^2$), and age at menopause for postmenopausal women. All models were stratified by menopausal status to assess effect measure modification. *P* for trend statistics were determined by the *p*-value for the coefficient of the continuous exposure variable, while adjusting for covariates.

Results

Descriptive characteristics of subjects stratified by menopausal status are depicted in Table 6. Cases were born on average 1 km closer to a USAEC site than controls. For postmenopausal women, cases were born about 0.5km closer than controls.

The associations between proximity to USAEC sites at birth and subsequent breast cancer are shown in Table 7. In premenopausal women, proximity within 3.3 kilometers of a USAEC site was suggestive of a slight increase in the odds ratio of breast cancer

(adjusted OR = 1.69, 95% CI = 0.68-4.21), although there were few women in this category. There was no evidence of a linear association with distance. A similar pattern was also seen with the postmenopausal women with a slightly raised breast cancer OR for subjects with birth residences within 3.3 km of their closest USAEC site (adjusted OR = 1.30, 95% CI = 0.43-3.99). Nevertheless, the confidence intervals for both pre- and postmenopausal women are also consistent with no increase in breast cancer risk.

As previously mentioned, the 13 USAEC sites were engaged in various uranium processing activities and the potential for the general population to be exposed to radionuclides and radiation from these sites may have differed depending on the activities at that site. However, proximity to either waste storage facilities or uranium enrichment/metal processing sites at the time of birth was not associated with breast cancer in either pre- or postmenopausal women (data not shown).

In Table 8, ORs and 95% CI for proximity of subjects' addresses at menarche to the closest USAEC site are shown. There were no consistent associations with proximity to these sites and risk for this time period of exposure. For premenopausal women, residing within 3.3 km of a USAEC site at menarche compared with women residing 15 km or greater at menarche the OR was 1.42 (95% CI = 0.46-4.34). There was, however, an apparent reduction in the OR for distances between 3.3 and 10.2 km. For postmenopausal women, proximity <15 km was associated with a reduction in the OR. For postmenopausal women residing within 3.3 km of an USAEC sites, the OR was 0.54 (95% CI = 0.28-1.02). Proximity of residence at first birth was also not consistently associated with subsequent breast cancer in either pre- or postmenopausal women (Table 9).

We used the radiological surveys and RESRAD 7.0 code (Argonne National Laboratory, Argonne, IL.) to estimate whole body doses of ionizing radiation from on-site contamination with uranium-238, uranium-235, radium-226, and thorium-232. In a worst case scenario, an individual residing on a premises of a $1000m^2$, with the average concentration of radionuclides estimated from the Linde Plant, would have an Effective Dose Equivalent of 0.42 mSv/year, which is within the range of background radiation exposure experienced by the general population (3.6 mSv/yr).[24]

Table 1. Descriptive Characteristics (means (SD) and percentages) of Study Participants Born in Erie and Niagara Counties between 1942 and 1964.

Variable	Premenopausal			Postmenopausal		
	Cases (*n*=160)	Controls (*n*=281)	P-value	Cases (*n*=104)	Controls (*n*=143)	P-value
Age (years)*	44.26 (4.51)	43.68 (4.37)	0.18	53.07 (3.05)	50.39 (3.29)	<0.0001
Education (years)*	13.71 (2.15)	14.24 (2.30)	0.01	14.07 (2.39)	13.64 (2.31)	0.16
Age at Menarche (years)*	12.52 (1.48)	12.56 (1.65)	0.79	12.08 (1.58)	12.45 (1.61)	0.07
Age at Menopause (years)*	--	--		48.32 (4.29)	45.41 (5.67)	<0.0001
Age at First Birth (years)*	19.76 (10.03)	21.58 (10.74)	0.80	19.14 (9.92)	19.78 (9.72)	0.61
Body Mass Index*	27.36 (7.15)	27.23 (6.19)	0.84	25.59 (5.43)	28.89 (7.32)	0.71
Distance to Closest Site (km)*	11.30 (6.21)	12.58 (7.96)	0.06	10.19 (5.89)	10.76 (7.39)	0.50
Parity (%)						
0 births	15%	17%		18%	17%	
1-2 births	59%	54%		51%	46%	
3+ births	26%	28%	0.62	31%	37%	0.59

Table 6, continued. Descriptive Characteristics (means (SD) and percentages) of Study Participants Born in Erie and Niagara Counties between 1942 and 1964.

Variable	Premenopausal			Postmenopausal		
	Cases (*n*=160)	Controls (*n*=281)	P-value	Cases (*n*=104)	Controls (*n*=143)	P-value
First-degree Relative with Breast Cancer (% yes)	23%	9%	0.0002	16%	7%	0.02
Benign Breast Disease (% yes)	34%	22%	0.01	39%	25%	0.02

* Mean (standard deviation)

** T-tests were used to calculate p-values for continuous variables and χ^2 tests were used for categorical variables

Table 2. Odds Ratios and 95% Confidence Intervals for Birth Address Distance to the Closest US Atomic Energy Commission Site.

	Premenopausal				Postmenopausal			
Distance (km)	Cases (*n*=160)	Controls (*n*=281)	Crude OR (95%CI)	Adjusted OR (95%CI)*	Cases (*n*=104)	Controls (*n*=143)	Crude OR (95%CI)	Adjusted OR (95%CI)*
>14.87	35	90	1.00	1.00	14	28	1.00	1.00
10.21-14.86	57	63	2.33 (1.37-3.95)	2.20 (1.25-3.89)	29	40	1.45 (0.65-3.23)	1.80 (0.68-4.71)
6.60-10.20	26	60	1.11 (0.61-2.04)	0.96 (0.51-1.82)	35	33	2.12 (0.95-4.71)	1.69 (0.66-4.32)
3.30-6.60	30	54	1.43 (0.79-2.59)	1.36 (0.73-2.55)	15	21	1.43 (0.57-3.59)	1.56 (0.51-4.83)
<3.30	12	14	2.20 (0.93-5.23)	1.69 (0.68-4.21)	11	21	1.05 (0.40-2.77)	1.30 (0.43-3.99)
P for trend				0.2236				0.6613

* Adjusted for age, race, education, previous benign breast disease, parity, age at first birth, age at menarche, BMI, age at first birth, family history of breast cancer, and age at menopause for postmenopausal women only.

Table 3. Odds Ratios and 95% Confidence Intervals for Menarche Address Distance to the Closest US Atomic Energy Commission Site.

Distance (km)	Premenopausal				Postmenopausal			
	Cases (*n*=204)	Controls (*n*=386)	Crude OR (95%CI)	Adjusted OR (95%CI)*	Cases (*n*=377)	Controls (*n*=532)	Crude OR (95%CI)	Adjusted OR (95%CI)*
>14.87	78	147	1.00	1.00	95	122	1.00	1.00
10.21-14.86	62	88	1.32 (0.87-2.03)	1.30 (0.82-2.04)	98	149	0.85 (0.58-1.22)	0.72 (0.48-1.06)
6.60-10.20	33	96	0.65 (0.40-1.05)	0.65 (0.39-1.08)	90	130	0.89 (0.61-1.30)	0.70 (0.47-1.05)
3.30-6.60	25	46	1.02 (0.59-1.79)	0.94 (0.52-1.70)	72	96	0.96 (0.64-1.45)	0.76 (0.49-1.17)
<3.30	6	9	1.26 (0.43-3.67)	1.42 (0.46-4.34)	22	35	0.81 (0.44-1.47)	0.54 (0.28-1.02)
P for trend				0.3978				0.1937

* Adjusted for age, race, education, previous benign breast disease, parity, age at first birth, age at menarche, BMI, age at first birth, family history of breast cancer and age at menopause for postmenopausal women only.

Table 4. Odds Ratios and 95% Confidence Intervals for First Birth Address Distance to the Closest US Atomic Energy Commission Site.

	Premenopausal				Postmenopausal			
Distance (km)	Cases (*n*=181)	Controls (*n*=371)	Crude OR (95%CI)	Adjusted OR (95%CI)*	Cases (*n*=434)	Controls (*n*=768)	Crude OR (95%CI)	Adjusted OR (95%CI)*
>14.87	79	171	1.00	1.00	133	211	1.00	1.00
10.21-14.86	36	77	1.01 (0.63-163)	0.95 (0.56-1.59)	109	247	0.70 (0.51-0.96)	0.70 (0.50-0.97)
6.60-10.20	38	78	1.06 (0.66-1.69)	1.14 (0.70-1.86)	116	174	1.06 (0.77-1.46)	1.01 (0.72-1.41)
3.30-6.60	25	39	1.33 (0.79-2.45)	1.34 (0.74-2.43)	57	104	0.87 (0.59-1.28)	0.86 (0.57-1.30)
<3.30	3	6	1.08 (0.26-4.44)	0.89 (0.20-4.06)	19	32	0.94 (0.51-1.73)	1.09 (0.57-2.08)
P for trend				0.7820				0.2726

*Adjusted for age, race, education, previous benign breast disease, parity, age at first birth, age at menarche, BMI, age at first birth, family history of breast cancer and age at menopause for postmenopausal women only.

C. Proximity to Chemical or Primary Metal Industrial Sites

Women living in urban environments are at greater risk of breast cancer than those in rural settings; this difference is not well understood. We conducted a study to examine environmental exposures 10 and 20 years prior to diagnosis (cases) or interview (controls) in relation to breast cancer risk, in particular risk associated with: 1) residential proximity to chemical industry sites; 2) residential proximity to primary metal industry sites. It's a population-based case control study. Cases were women, age 35-79 with incident, primary, histologically confirmed breast cancer living in Erie or Niagara counties; controls were population based, frequency matched to cases on age, race and county. Self-reported lifetime residential histories were collected, and missing address information supplemented with Polk Directory searches. 863 cases and 1579 controls with complete residential addresses for the periods 10 and 20 years prior to diagnosis (or interview for controls) were included in these analyses. Industrial directories for New York State for 1978 and 1988, were used to identify chemical and primary metal factories operating in this region. The chemical facility in our study includes Standard Industrial Classification (SIC) groups 28 (chemicals and allied products), 29 (petroleum refining and related industries), and 30 (rubber and miscellaneous plastics products); and primary metal facility includes SIC 33. We used ArcView3.2 (using GDT/Dynamap as the base map) to geocode the addresses. The locations of industrial sites and residences are list in Figure 1 and 2. Quartiles were created to categorize the distance from residential address to the closest industrial site; women living within 0.25 mile of a facility were put in a separate category. We used logistic regression to calculate the odds ratios and 95% confidence intervals, adjusting for age, education, race, BMI, age at first birth, age at menarche, age at menopause (postmenopausal women), parity, first-degree relative with breast cancer, and previous benign breast disease. For both pre and postmenopausal women, no evidence that living close to chemical or primary metal facility 10 and 20 years ago was associated with increased risk (Tables 1 to 4). In this study, we used proximity to estimate exposure. However, the complexity of the chemical mixtures from different sites likely leads to exposure misclassification. While our measure of exposure to any single compound is crude, the real world exposure is generally to mixtures of compounds. In this study we found no effect of exposure to these mixtures in the recent decades on breast cancer risk.

Figure 1. Locations of Industries and Residence by Case-control Status, Premenopausal Women

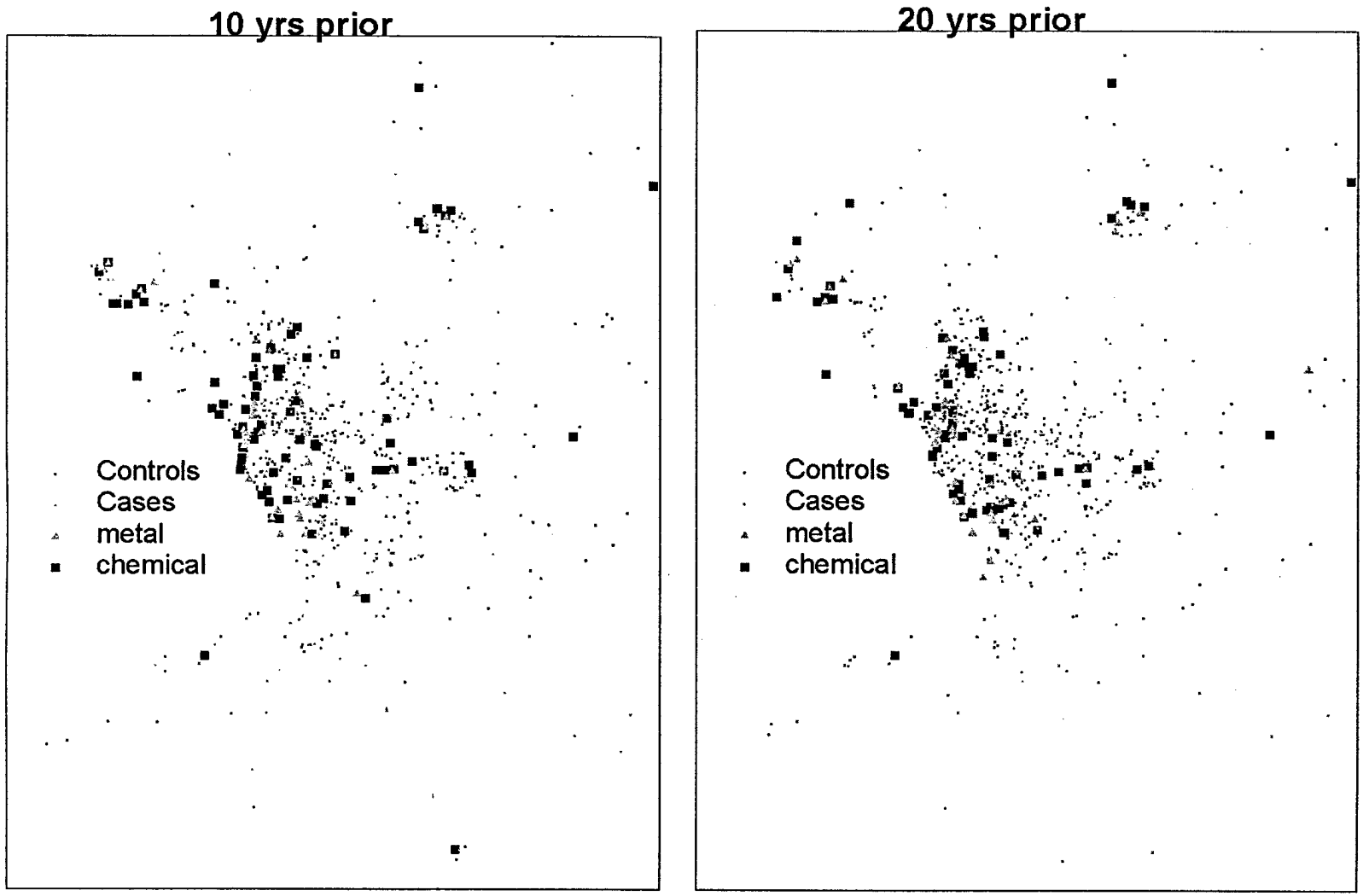


Figure 2. Locations of Industries and Residence by Case-control Status, Postmenopausal Women

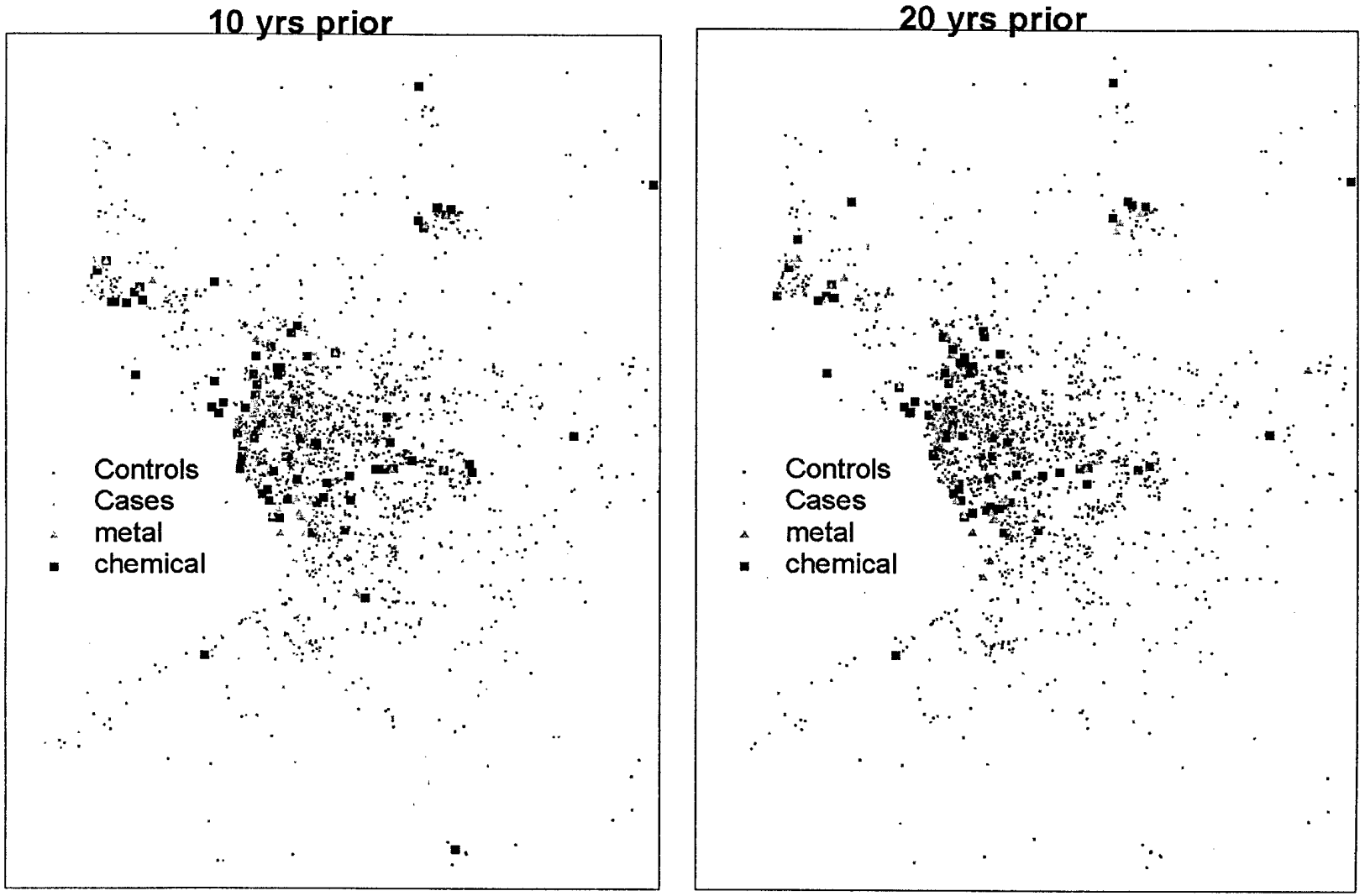


Table 1. Residential proximity to chemical facility 20 yrs ago and Risk of Breast Cancer

Categories of Distance	Cases	Controls	Crude OR	Adjusted OR* (CI)	P for trend
		Pre-menopausal			
1: >2.22 miles	**61**	**98**	**1.00**	**1.00**	
2: 1.16-2.22	**35**	**97**	**0.58 (0.35-0.96)**	**0.55 (0.32-0.93)**	
3: 0.71-1.16	**51**	**101**	**0.81 (0.51-1.29)**	**0.79 (0.48-1.30)**	
4: 0.25-0.71	**47**	**86**	**0.88 (0.54-1.42)**	**0.83 (0.49-1.40)**	
5: <=0.25mile	**7**	**13**	**0.87 (0.33-2.29)**	**0.95 (0.34-2.62)**	**0.06**
		Post-menopausal			
1: >2.99miles	**179**	**296**	**1.00**	**1.00**	
2: 1.41-2.99	**159**	**295**	**0.89 (0.68-1.17)**	**0.86 (0.65-1.13)**	
3: 0.78-1.41	**161**	**291**	**0.92 (0.70-1.20)**	**0.91 (0.69-1.20)**	
4: 0.25-0.78	**143**	**267**	**0.89 (0.67-1.17)**	**0.90 (0.67-1.21)**	
5: <=0.25mile	**20**	**35**	**0.95 (0.53-1.69)**	**0.84 (0.46-1.54)**	**0.68**

* **Odds ratios and 95% confidence intervals adjusted for age, education, race, BMI (1 yr before interview), age at first birth, age at menarche, age at menopause (for post-menopausal women only), number of births, first-degree relative with breast cancer, and previous benign breast disease.**

Table 2. Residential proximity to chemical facility 10 yrs ago and Risk of Breast Cancer

Categories of Distance	Cases	Controls	Crude OR	Adjusted OR* (CI)	P for trend
		Pre-menopausal			
1: >2.53 miles	**50**	**98**	**1.00**	**1.00**	
2: 1.07-2.53	**49**	**99**	**0.97 (0.60-1.57)**	**0.93 (0.56-1.54)**	
3: 0.65-1.07	**58**	**98**	**1.16 (0.73-1.86)**	**1.25 (0.76-2.06)**	
4: 0.25-0.65	**35**	**88**	**0.78 (0.46-1.31)**	**0.82 (0.47-1.43)**	
5: <=0.25mile	**9**	**12**	**1.47 (0.58-3.72)**	**1.72 (0.64-4.59)**	**0.45**
		Post-menopausal			
1: >2.50miles	**167**	**296**	**1.00**	**1.00**	
2: 1.10-2.50	**171**	**295**	**1.03 (0.79-1.34)**	**1.05 (0.80-1.39)**	
3: 0.65-1.07	**157**	**295**	**0.94 (0.72-1.24)**	**0.95 (0.71-1.26)**	
4: 0.25-0.65	**138**	**253**	**0.97 (0.73-1.28)**	**1.00 (0.75-1.35)**	
5: <=0.25mile	**29**	**45**	**1.14 (0.69-1.89)**	**1.28 (0.76-2.16)**	**0.64**

* **Odds ratios and 95% confidence intervals adjusted for age, education, race, BMI (1 yr before interview), age at first birth, age at menarche, age at menopause (for post-menopausal women only), number of births, first-degree relative with breast cancer, and previous benign breast disease.**

Table 3. Residential proximity to primary metal industry 20 yrs ago and Risk of Breast Cancer

Categories of Distance	Cases	Controls	Crude OR	Adjusted OR* (CI)	P for trend
		Pre-menopausal			
1: >2.95 miles	**61**	**98**	**1.00**	**1.00**	
2: 1.62-2.95	**48**	**99**	**0.78 (0.49-1.25)**	**0.77 (0.47-1.26)**	
3: 0.91-1.62	**51**	**99**	**0.83 (0.52-1.32)**	**0.82 (0.50-1.34)**	
4: 0.25-0.91	**39**	**87**	**0.72 (0.44-1.18)**	**0.74 (0.43-1.26)**	
5: <=0.25mile	**2**	**12**	**0.27 (0.06-1.24)**	**0.22 (0.05-1.06)**	**0.14**
		Post-menopausal			
1: >3.61miles	**167**	**296**	**1.00**	**1.00**	
2: 2.02-3.61	**178**	**294**	**1.07 (0.82-1.40)**	**0.99 (0.75-1.31)**	
3: 1.16-2.02	**154**	**292**	**0.94 (0.71-1.23)**	**0.96 (0.72-1.28)**	
4: 0.25-1.16	**151**	**286**	**0.94 (0.71-1.23)**	**0.90 (0.67-1.20)**	
5: <=0.25mile	**12**	**16**	**1.33 (0.61-2.88)**	**1.45 (0.65-3.23)**	**0.62**

* **Odds ratios and 95% confidence intervals adjusted for age, education, race, BMI (1 yr before interview), age at first birth, age at menarche, age at menopause (for post-menopausal women only), number of births, first-degree relative with breast cancer, and previous benign breast disease.**

Table 4. Residential proximity to primary metal industry 10 yrs ago and Risk of Breast Cancer

Categories of Distance	Cases	Controls	Crude OR	Adjusted OR* (CI)	P for trend
		Pre-menopausal			
1: >3.80 miles	**46**	**98**	**1.00**	**1.00**	
2: 1.66-3.80	**59**	**99**	**1.27 (0.79-2.04)**	**1.37 (0.83-2.26)**	
3: 1.06-1.66	**51**	**98**	**1.11 (0.68-1.80)**	**1.06 (0.63-1.78)**	
4: 0.25-1.06	**43**	**93**	**0.99 (0.60-1.63)**	**1.07 (0.62-1.85)**	
5: <=0.25mile	**2**	**7**	**0.61 (0.12-3.05)**	**0.49 (0.09-2.58)**	**0.97**
		Post-menopausal			
1: >3.59miles	**164**	**295**	**1.00**	**1.00**	
2: 2.02-3.59	**164**	**295**	**1.00 (0.76-1.31)**	**0.94 (0.71-1.24)**	
3: 1.12-2.02	**171**	**297**	**1.04 (0.79-1.35)**	**1.02 (0.77-1.35)**	
4: 0.25-1.12	**152**	**283**	**0.97 (0.73-1.27)**	**0.99 (0.73-1.33)**	
5: <=0.25mile	**11**	**14**	**1.41 (0.63-3.19)**	**1.69 (0.73-3.90)**	**0.41**

* **Odds ratios and 95% confidence intervals adjusted for age, education, race, BMI (1 yr before interview), age at first birth, age at menarche, age at menopause (for post-menopausal women only), number of births, first-degree relative with breast cancer, and previous benign breast disease.**

Task 2: To examine estimated exposure to benzene and PAHs as a risk factor for pre-and postmenopausal breast cancer, with control for appropriate confounders.

We have geocoded industrial sites, especially major PAH emitters for several decades and will continue with this work for the other relevant periods. We are also working on the development of geographic models to estimate historical PAH exposure from traffic and industrial sites.

We have completed data analysis examining early life exposure to total suspended particulates and exposure to environmental tobacco smoke in relation to risk of breast cancer in adult life. We are interested in both of these exposures as proxies for exposure to PAHs and benzene. Currently manuscripts for these analyses are in preparation and will be submitted for publication in the next several months.

A. Early Life Exposure to PAHs and Breast Cancer Risk.

Polycyclic aromatic hydrocarbons (PAHs) are ubiquitous in the environment and commonly present in air pollution.[25,26] PAHs are a broad category of chemical compounds composed of carbon and hydrogen and are formed as a by-product during combustion of organic materials. Important sources of PAHs include cigarette smoke, steel mills, foundries, automobiles, electricity production and many other industrial and non-industrial processes. PAHs are also found in food and are formed when food is cooked at high temperatures (i.e., grilling meats). In addition to anthropogenic sources, natural sources (i.e., volcanoes and forest fires) also contribute PAHs to the atmosphere.[25,27] Most of these sources not only contribute to the release of PAHs into the environment, but also contribute to particulate air pollution. Ninety to 95% of particulate phase PAHs are physically associated with particulate matter less than 3.3 μm.[26,28] These small particles are thought to have particular biologic relevance since they can be inhaled and deposited in the lower respiratory tract.[29] There is evidence from animal models that PAHs are skin and mammary carcinogens.[25,30,31] PAHs are lipophilic[32,33] and may be human mammary carcinogens.[34,35] Additionally, PAHs may also have endocrine disruptive properties which could potentially affect breast cancer risk.[36]

Few epidemiologic investigations of breast cancer have examined PAHs in relation to risk. Petralia and co-authors[37] examined premenopausal breast cancer and occupational exposure to benzene and PAHs using job-exposure matrices in a population-based, case-control study. High probability of exposure to benzene and PAHs was associated with premenopausal breast cancer. However, because women were exposed to more than one compound, it was difficult to estimate whether PAHs had an independent effect.

Recently, Rundle et al.[35] examined PAH-DNA adducts in breast tumor tissue. They found a 2-fold increase in PAH-DNA adducts in malignant tumors compared with benign breast disease with atypia controls. Gammon et al.[34] examined PAH-DNA adducts in mononuclear cells in relation to the risk of breast cancer in a case-control study of Long Island residents. They found a nearly 50% increase in the risk of breast cancer for subjects in the highest quintile of PAH-DNA adducts in mononuclear cells; there was no dose-response relationship.

Early life exposures, including PAHs, may have particular importance in the etiology of breast cancer. Early age at exposure to ionizing radiation, for example, confers increased risk of breast cancer when compared with later age at exposure.[3,7] In addition, several other established risk factors also indicate the importance of early life factors in the etiology of breast cancer. Breast cancer risk is increased in women with early age at menarche (<12 yrs), whereas early age at first birth reduces the risk of breast cancer. The physiological changes that occur to breast tissue during development further support the postulation that early life exposures may be important. Around menarche, the mammary gland begins to develop and differentiate into defined ducts and lobules. The primary lobules formed at this time are type 1 lobules. These lobules will further differentiate into type 2 and type 3 lobules. This differentiation of type 1 lobules to type 2 lobules and then to type 3 lobules is brought on by pregnancy.[38] *In vitro* studies have shown that cells from type 1 lobules are more sensitive to proliferation signals than cells from type 2 or 3 lobules.[39] In addition, human breast epithelial cells from type 1 lobules were more sensitive to the transforming effects of the PAH, 7,12-dimethlybenzo(a)anthracene and N-methyl-N-nitrosourea than were type 3 lobule cells.[40] Further, Russo et al.[38] have shown that type 1 lobules in nulliparous women are equivalent to the terminal ductal lobular unit, where carcinoma originates in breast epithelium.

We conducted a population-based, case-control study of PAH exposure in early life in relation to the risk of breast cancer. For this study we used total suspended particulates (TSP), a measure of ambient air pollution, as a proxy for PAH exposure. We hypothesized that PAHs are human mammary carcinogens and that women exposed to high concentrations of PAHs in air pollution will have greater risk of breast cancer compared with women exposed to lower concentrations of TSP. We examined time periods that are thought to be critical exposure periods with regards to susceptibility to breast cancer; at the time of birth, menarche, and first birth.

Exposure Assessment

The New York State Department of Environmental Conservation maintains monitors measuring total suspended particulates (TSP) beginning in 1959. These monitors measured TSP concentrations every seven days. Annual average TSP concentrations (1959-1997) were obtained from these monitors for Eire and Niagara Counties. In total, 87 monitors were operating at various times in Erie and Niagara Counties during this time period. For the period of the 1960's, average TSP concentrations were calculated for the entire decade for each monitor. During this time period, there were fewer monitors operating than at later time periods. There was very little within monitor variation of TSP concentration during this time period and by averaging the TSP concentrations for each monitor, the overall TSP estimates were more stable. Considerably more monitors were operating in the years after 1969. Annual average TSP concentrations were calculated for each year for 1970 through 1997 for each monitor.

Based on the monitor readings for each time period, prediction maps of TSP concentrations were generated with ArcGIS 8.0 (ESRI, Inc., Redlands, CA) using inverse distance squared weighted interpolation. We assumed a 45-degree angle to account for the prevailing north easterly winds and limited the exposure estimation to the seven closest sampling monitors. The primary assumption of these geostatistical methods is

that close locations are more similar to one another than are locations relatively farther away.[41] The estimated individual residential TSP concentrations were insensitive to changing the number monitors included for the exposure estimation. In total, 29 prediction maps were constructed of estimated TSP concentrations for the two county region; one for the 1960's and one for each year after that until 1997. These maps were used to determine exposure to TSP at each participant's address for the year(s) when the participant resided at that particular address. The 1960's TSP concentration prediction map is provided as an example in figure 1.

TSP concentrations for addresses before the 1960s were estimated assuming that the interpolated concentrations in the 1960s were representative of earlier time periods. Measures to control air quality were implemented in the early 1970's. Industrialization in Erie and Niagara Counties began at the end of the 19th century and the industrial activities that contributed most heavily to air pollution were very active prior to the 1960's and thought to be relatively constant over the time period.[42] Consequently, the 1960's concentrations of TSP probably reflect ambient levels in the earlier time period.

Statistical Analysis

Unconditional logistic regression[23] was used to estimate odds ratios (OR) and 95% confidence intervals (95% CI). TSP concentrations were categorized into 4 levels (<84 ug/m^3, 84-114 ug/m^3, 115-140ug/m^3, and >140ug/m^3). The cut points for the categorical analyses were derived from the quartiles of the distribution of measurements of TSP concentrations in the 1960s. In addition to the categorical analysis, we examined TSP concentrations as a continuous variable. Further, logistic quadratic spline regression with knots at 100 μg/m^3 and 135 μg/m^3 was used to graphically depict the exposure-response trend; the estimated probability of being a case was calculated from the quadratic spline regression equation. The end categories were restricted to linear segments to prevent instability.[43] The values for the two knots in the spline regression were selected based on a previous categorical analysis.

We considered age, race, education, age at first birth, age at menarche, parity, previous benign breast disease, family history of breast cancer, body mass index (weight (kg)/height (m) ^{2}), and age at menopause as potential confounders in multivariate logistic regression. The model presented include age, education, and parity and was determined by excluding variables from the full model which did not alter the risk estimates more than 10%. All models were stratified by menopausal status to assess effect modification. *P* for trend statistics were determined by the *p*-value for the coefficient of the continuous exposure variable, while adjusting for covariates.

Results

The descriptive characteristics of the participants included in the birth, menarche, first birth, and the overall case-control study are depicted in Table 1. No major differences were observed between the distributions of these variables between each time period. We were able to successfully geocode 79%, 87%, and 87% of the Erie and Niagara County birth, menarche, and first birth addresses, respectively.

Exposure to concentrations of TSP above the referent at the time of birth was associated with an increase in the odds ratio for premenopausal women (Table 2), although the *P* for trend was not significant. In addition, there were relatively few participants exposed to the lowest concentrations of TSP and confidence intervals were

wide. In postmenopausal women, exposure to high concentrations of TSP (>140 $\mu g/m^3$) was associated with an adjusted OR of 2.75 (95% CI=1.04-7.26) compared with exposure to low concentrations (<84 $\mu g/m^3$), although the 95% confidence intervals were relatively wide due to the relatively small numbers in the referent category. For risk associated with estimated residential TSP concentrations as a continuous variable, in postmenopausal women, we observed a 21% increase in the odds ratio for every 30 $\mu g/m^3$ increase in TSP concentration (adjusted OR = 1.21, 95% CI = 1.05-1.40). In the spline regression analysis, there was an increase in the probability of being a case with an increase in TSP concentration (Figure 2). No increase in risk was observed for premenopausal women on a continuous scale (OR = 0.91, 95% CI = 0.75-1.11for every increase in 30$\mu g/m^3$ of TSP). Further, the spline regression analysis for the premenopausal women indicated an inverted parabola exposure-response relationship with increasing TSP concentration (Figure 3).

Exposure to high concentrations of TSP at menarche was also associated with a modest increase in the odds ratio for postmenopausal women with exposure > 84 $\mu g/m^3$, although the *P* for trend was not significant (Table 3). In the continuous analysis, for every 30 $\mu g/m^3$ increase in TSP concentrations, the odds ratio increased 8% (adjusted OR = 1.08, 95% CI = 0.96-1.21) for postmenopausal women. The risk estimates for the premenopausal women were not consistent with our hypothesis. In this group, the highest exposure category was observed to have a reduced OR (adjusted OR = 0.66, 95% CI = 0.38-1.16), although the confidence interval was wide. Exposure to high concentrations of TSP at the time of first birth was also associated with a modest increase in the odds ratio for postmenopausal women (Table 4). For premenopausal women exposed to high concentration of TSP, there was some indication of a reduction in the odds ratio (OR = 0.52, 95% CI = 0.22-1.20), although the confidence interval was wide and included the null.

Figure 1. Total Suspended Particulate Concentrations in Erie and Niagara Counties, Western New York (1960's).

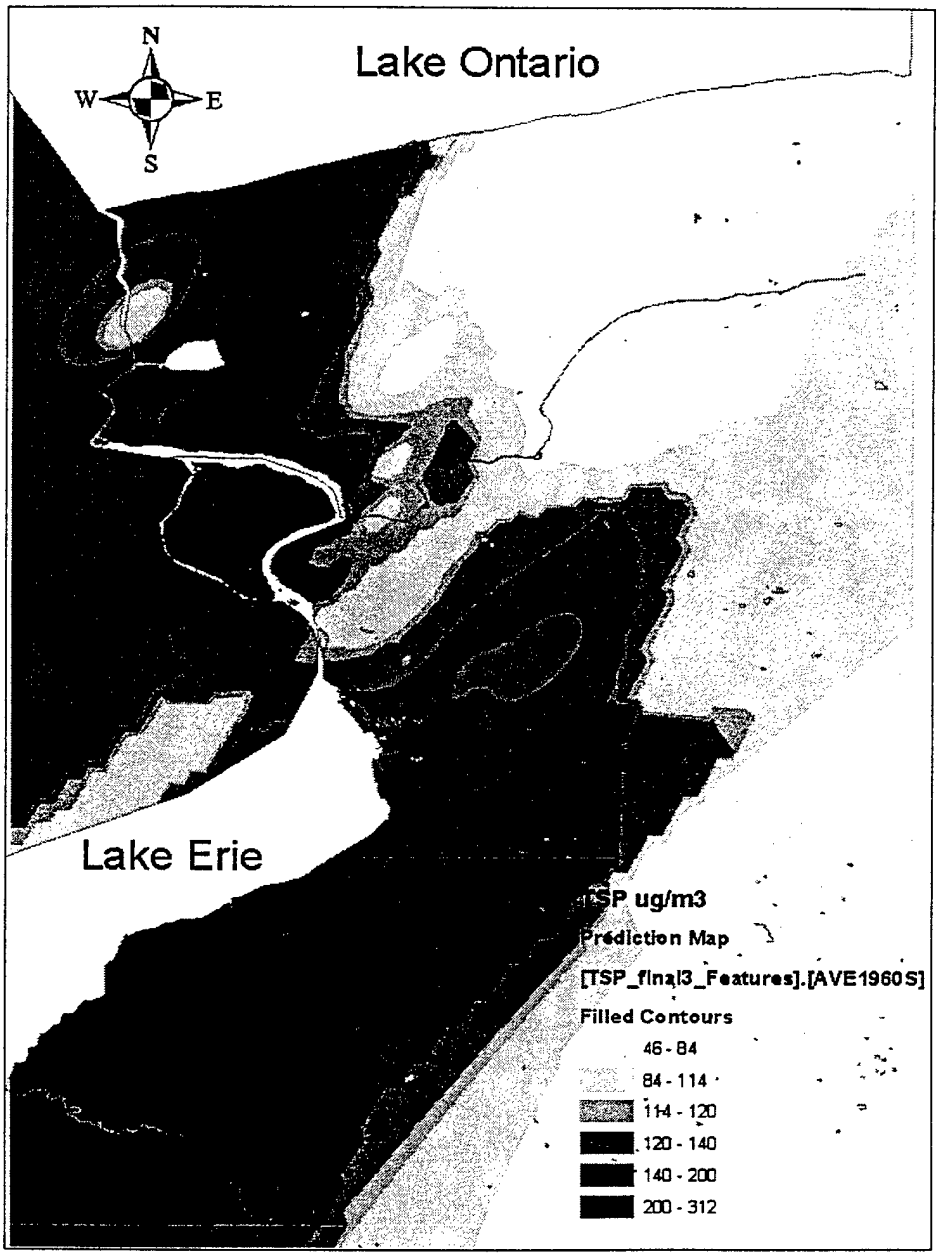


Figure 2. Estimated Probability of Being a Case for Postmenopausal Women by Total Suspended Particulate Concentration at Birth Address.

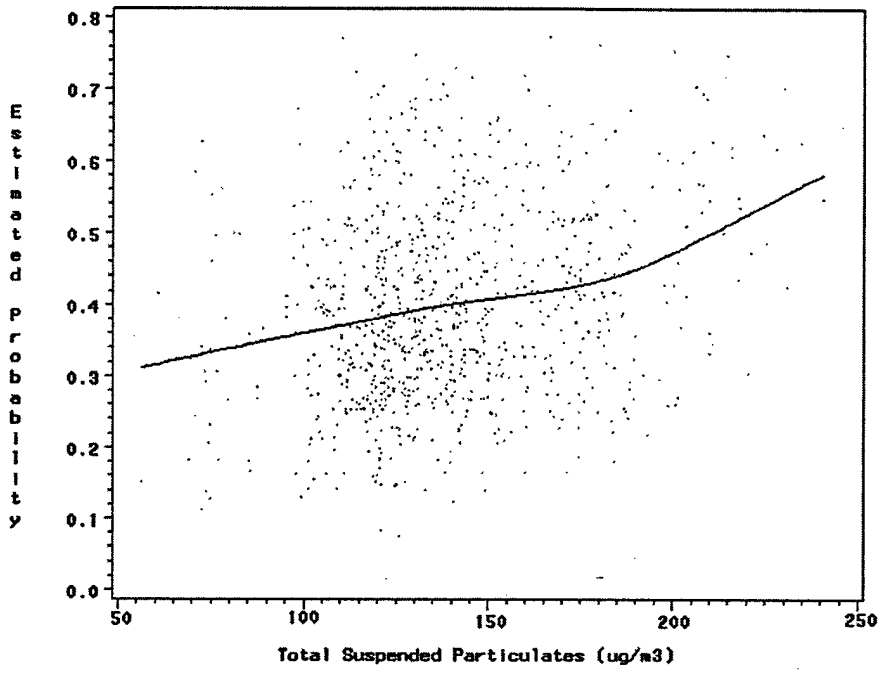


Figure 3. Estimated Probability of Being a Case for Premenopausal Women by Total Suspended Particulate Concentration at Birth Address.

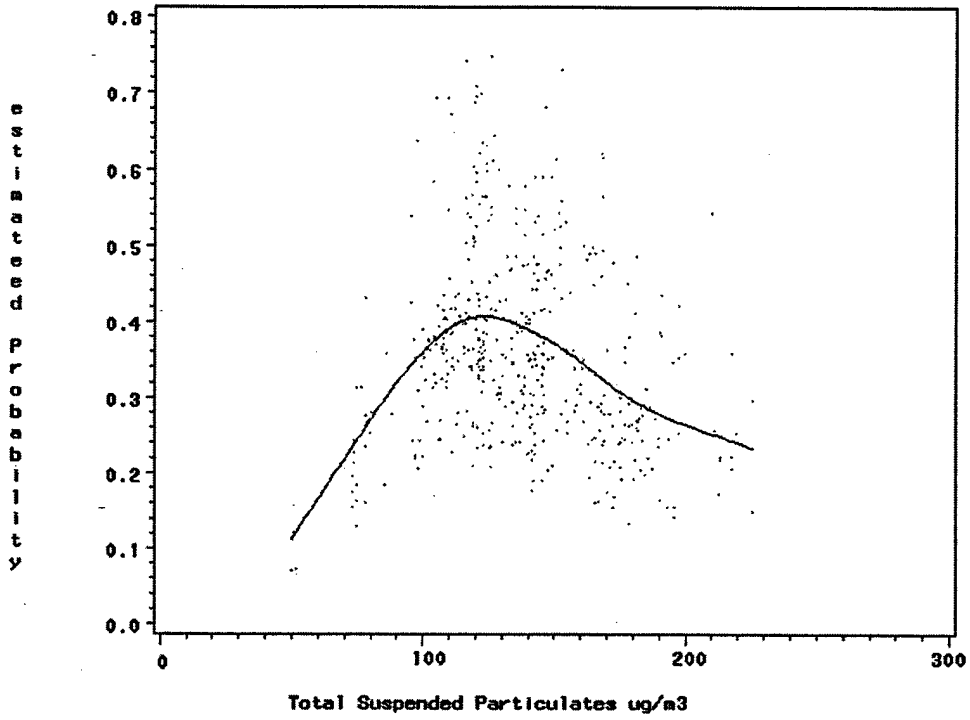


Table 1. Descriptive Characteristics for Study Participants at Birth, Menarche, First Birth, and Overall Study.

	Premenopausal Women							
	Birth		Menarche		First Birth		Overall Study	
	Cases (*n*=160)	Controls (*n*=283)	Cases (*n*=204)	Controls (*n*=386)	Cases (*n*=181)	Controls (*n*=371)	Cases (*n*=325)	Controls (*n*=610)
Age	44.3 (4.5)	43.8 (4.5)	44.5 (4.5)	43.8 (4.6)	44.5 (4.7)	44.2 (4.6)	44.9 (4.6)	44.1 (4.6)
Education	13.7 (2.2)	14.2 (2.2)	13.9 (2.0)	14.1 (2.2)	13.9 (2.0)	14.1 (2.1)	14.0 (2.3)	14.2 (2.2)
Age at Menarche	12.5 (1.5)	12.6 (1.6)	12.5 (1.6)	12.6 (1.6)	12.5 (1.4)	12.7 (1.6)	12.5 (1.6)	12.6 (1.6)
Age at First Birth	25.1 (4.8)	26.1 (4.5)	25.4 (4.9)	25.7 (4.8)	25.7 (7.2)	26.1 (4.9)	25.0 (5.1)	25.8 (4.8)
Body Mass Index	27.4 (7.2)	27.3 (6.3)	27.0 (6.9)	27.6 (6.8)	27.2 (7.2)	27.3 (6.6)	27.2 (6.8)	27.6 (6.7)
Benign Breast Disease (yes)	34%	22%	35%	20%	35%	22%	37%	21%
1° Relative with Breast Cancer (yes)	23%	10%	23%	10%	21%	9%	21%	10%

Table 1, continued. Descriptive Characteristics for Study Participants at Birth, Menarche, First Birth, and Overall Study.

	Postmenopausal Women							
	Birth		Menarche		First Birth		Overall Study	
	Cases (*n*=345)	Controls (*n*=521)	Cases (*n*=469)	Controls (*n*=757)	Cases (*n*=435)	Controls (*n*=782)	Cases (*n*=841)	Controls (*n*=1495)
Age	62.2 (7.8)	62.01 (9.1)	61.9 (8.1)	62.2 (9.1)	62.8 (8.3)	63.0 (8.9)	63.0 (8.5)	63.4 (8.9)
Education	13.4 (2.5)	13.0 (2.1)	13.4 (2.5)	13.0 (2.1)	13.2 (2.4)	13.0 (2.2)	13.3 (2.6)	13.0 (2.3)
Age at Menarche	12.4 (1.5)	12.8 (1.4)	12.5 (1.5)	12.8 (2.1)	12.6 (1.6)	12.8 (1.7)	12.6 (1.6)	12.8 (1.7)
Age at First Birth	23.9 (4.4)	23.7 (3.9)	23.9 (4.5)	23.7 (6.3)	24.3 (4.8)	24.1 (4.4)	23.8 (4.7)	23.5 (4.3)
Body Mass Index	28.6 (5.9)	28.4 (6.1)	28.6 (5.8)	26.7 (6.3)	28.9 (5.8)	28.5 (5.9)	28.9 (6.0)	28.5 (6.1)
Age at Menopause	48.3 (5.0)	47.4 (6.0)	48.0 (5.3)	47.6 (6.0)	45.9 (5.6)	47.6 (6.0)	48.3 (5.4)	47.4 (6.3)
Benign Breast Disease (yes)	35%	22%	34%	23%	34%	21%	33%	22%
1° Relative with Breast Cancer (yes)	20%	14%	19%	15%	21%	13%	20%	14%

Table 2. Risk associated with exposure to Total Suspended Particulate Concentrations at Birth Address: Western New York Breast Cancer Case-Control Study.

	Premenopausal				Postmenopausal			
TSP ug/m^3	Cases (n=160)	Controls (n=283)	Crude OR (95%CI)	Adjusted OR (95%CI)*	Cases (n=345)	Controls (n=521)	Crude OR (95%CI)	Adjusted OR (95%CI)*
<84	5	16	1.00	1.00	6	19	1.00	1.00
84-114	25	46	1.74 (0.57-5.31)	1.87 (0.61-5.77)	52	66	2.50 (0.93-6.70)	2.71 (0.98-7.45)
115-140	63	92	2.19 (0.76-6.29)	2.19 (0.76-6.31)	134	221	1.92 (0.75-4.93)	2.14 (0.81-5.65)
>140	67	129	1.66 (0.58-4.73)	1.72 (0.60-4.94)	153	215	2.25 (0.88-5.77)	2.75 (1.04-7.26)
P for Trend				0.3932				0.0088

* Adjusted for age, education, and parity.

Table 3. Risk associated with exposure to Total Suspended Particulate Concentrations at Menarche Address: Western New York Breast Cancer Case-Control Study.

	Premenopausal				Postmenopausal			
TSP ug/m^3	Cases (n=204)	Controls (n=386)	Crude OR (95%CI)	Adjusted OR (95%CI)*	Cases (n=469)	Controls (n=757)	Crude OR (95%CI)	Adjusted OR (95%CI)*
<84	32	66	1.00	1.00	14	28	1.00	1.00
84-114	53	99	1.10 (0.65-1.89)	0.98 (0.56-1.70)	81	120	1.35 (0.67-2.72)	1.36 (0.67-2.77)
115-140	62	81	1.58 (0.92-2.70)	1.25 (0.71-2.23)	171	298	1.15 (0.59-2.24)	1.20 (0.61-2.36)
>140	57	140	0.84 (0.50-1.42)	0.66 (0.38-1.16)	203	311	1.31 (0.67-2.54)	1.45 (0.74-2.87)
P for Trend				0.2114				0.1879

* Adjusted for age, education, and parity.

Table 4. Risk associated with exposure to Total Suspended Particulate Concentrations at First Birth Address: Western New York Breast Cancer Case-Control Study.

	Premenopausal				Postmenopausal			
TSP ug/m^3	Cases (n=181)	Controls (n=371)	Crude OR (95%CI)	Adjusted OR (95%CI)*	Cases (n=435)	Controls (n=782)	Crude OR (95%CI)	Adjusted OR (95%CI)*
<84	147	294	1.00	1.00	54	102	1.00	1.00
84-114	19	30	1.27 (0.69-2.33)	1.06 (0.55-2.02)	89	150	1.12 (0.74-1.71)	1.30 (0.83-2.03)
115-140	5	19	0.53 (0.19-1.44)	0.41 (0.14-1.67)	142	260	1.03 (0.70-1.52)	1.28 (0.83-1.97)
>140	10	28	0.71 (0.34-1.51)	0.52 (0.22-1.20)	150	270	1.05 (0.71-1.24)	1.33 (0.87-2.06)
P for trend				0.0378				0.6064

* Adjusted for age, education, and parity.

B. Environmental Tobacco Smoke Exposure in Early Life.

Tobacco smoke consists of numerous compounds that are carcinogenic, particularly to the lung [44-46]. Among these compounds are polycyclic aromatic hydrocarbons (PAHs) which are skin and mammary carcinogens in rodent models [25,30,31] and accumulate in adipose tissue including the breast [32,33]. The effect of tobacco smoke on breast cancer risk, however, is not clear. McMahon [47] hypothesized that tobacco smoke may reduce the risk of breast cancer because of the antiestrogenic effects of cigarette smoke. In particular, cigarette smoking is associated with postmenopausal osteoporosis and early onset of menopause; both conditions are related to low plasma concentrations of estrogen [48,49]. Conversely, Hiatt and Fireman [50] reasoned that smoking could increase breast cancer risk because mutagens from cigarette smoke concentrate in the breast fluid of nonlactating women. Additionally, cigarette smoking is associated with pancreatic, bladder and cervical cancers, all sites without direct contact between smoke and the organ's epithelium. Despite conflicting hypotheses about the effect of tobacco smoke on breast cancer risk, epidemiologic research has yet to demonstrate an association between cigarette smoking and breast cancer [51]. Further, there is limited evidence that environmental tobacco smoke (ETS) affects breast cancer risk [52,53].

Increasingly, there is interest that exposures in early childhood may be related to breast cancer risk [54-56] because of evidence that breast tissue may be more vulnerable to carcinogenic insults during this period when proliferation and differentiation of the terminal end buds initiates. Later, pregnancy and lactation result in further differentiation after which it seems that breast tissue is more resistant carcinogenic insults [38-40]. It has been hypothesized that exposures before a woman gives birth for the first time might be particularly important in relation to disease etiology. With regards to ETS, there have been a few studies; risk has been found to be increased in some [57], but not in all studies [58-60].

In this study, we explored exposure to ETS in early life in relation to the risk of subsequent breast cancer. Specifically, we hypothesized that residing with one or more household smokers in early life (up to age 21) would increase the risk of breast cancer compared with women who did not reside with household smokers.
Extensive in-person interviews and self-administered questionnaires were used to ascertain medical history, diet, lifetime alcohol consumption, residential history, occupational history, and smoking history. Questions about exposure to environmental tobacco smoke were asked for seven age periods: 1) <21 years, 2) 21-30, 3) 31-40, 4) 41-50, 5) 51-60, 6) 61-70, 7) >70. The number of people living with the participant who smoked cigarettes, cigars, or pipes during the specified time period was ascertained. In addition, participants were also asked for the number of years that they resided with these smokers. These two questions were used to compute person-years of ETS exposure for participants for each time period. For this study, we only considered exposure to ETS before the 21 years of age. Exposure to ETS were categorized into three groups: 1) no ETS exposure (0 person-years), 2) $\leq$20 person-years of ETS exposure, and 3) >20 person-years of ETS exposure. The cut point of 20 person-years of ETS exposure was derived from the median in the exposed controls.

As part of the interview, participants also completed a residential history listing each residence for their entire life that included information on the number of other people

who resided at each address and the number of those residents who smoked cigarettes. For analyses of exposure to household smokers at birth, menarche and the time of participant's first birth, only cases and controls that provided address information for the time of birth, menarche, and the time of first birth could be used. Additionally, cases and controls were restricted to those with complete household smoking information at both birth and menarche (n = 334 for cases and 609 for controls). Household smoking was categorized into a binary variable denoting either the presence or absence of household smokers.

Unconditional logistic regression [23] was used to calculate odds ratios (OR) and 95% confidence intervals (95% CI). Multiple logistic regression was used to assess potential confounding by age, race, education, age at first birth, age at menarche, parity, age at first birth, previous benign breast disease, family history of breast cancer in a first degree relative, body mass index (weight (kg)/ height (m) ^{2}), total lifetime alcohol consumption, and age at menopause for postmenopausal women only. All models were stratified by menopausal status to assess effect modification. Additional analyses were conducted excluding women who had never smoked to prevent active smoking from confounding any potential association between ETS and the risk of breast cancer. P for trend statistics were determined by the p-value for the coefficient of the continuous exposure variable, while adjusting for covariates.

Results

Demographic characteristics of the study participants by menopausal status are shown in table 1. Exposure to ETS before the age of 21 was associated with a 20-40% increase in the risk of breast cancer for both pre- and postmenopausal women (table 2); however, confidence intervals include the null. When the analysis was restricted to the sub-group of never smokers, similar results were obtained, although confidence intervals were wider because of decreased sample size (data not shown). For never smoking premenopausal women with >20 person-years of ETS exposure, the adjusted OR was 1.35 (95%CI = 0.76-2.39) when compared with women without any ETS exposure.

Associations between the presence of household smokers and breast cancer at birth and menarche residences are shown in table 3. Premenopausal women with breast cancer had some tendency to reside with one or more household smokers at their birth address more often than did controls (adjusted OR = 1.34, 95% CI = 0.77-2.32), while in postmenopausal women, the presence of household smokers was not associated with breast cancer (adjusted OR = 1.02, 95% CI = 0.68-1.55). Associations between the presence of household smokers at the time of menarche and breast cancer were similar.

The presence of household smokers at the time of a women's first birth was not associated with breast cancer in premenopausal women (adjusted OR = 1.11, 95% CI = 0.59-2.04). For postmenopausal women, however, exposure to household smoke at the time of first birth was suggestive, if anything, of a reduction in risk (adjusted OR = 0.71, 95% CI = 0.46-1.09) (Table 3). We attempted to examine each time period while adjusting for the other two time periods to investigate whether one time period in particular was associated with an increased odds ratio. However, household smoking status at each of the time periods was highly correlated and the results were uninterruptible.

Table 1. Descriptive Characteristics of Study Participants, Western New York Breast Cancer Study (1996-2001).

	Premenopausal		Postmenopausal	
	Cases (*n*=325)	Controls (*n*=610)	Cases (*n*=841)	Controls (*n*=1495)
Age				
35-45	176 (54%)	384 (63%)	7 (1%)	29 (2%)
46-55	149 (46%)	224 (37%)	175 (21%)	325 (22%)
56-65	-	2 (1%)	325 (39%)	403 (27%)
66-75	-	-	262 (31%)	630 (42%)
76+	-	-	72 (9%)	108 (7%)
Education				
<High school	2 (1%)	-	22 (3%)	38 (3%)
High school	105 (32%)	176 (32%)	388 (46%)	780 (52%)
>High school	218 (67%)	434 (71%)	431 (51%)	677 (45%)
Age at Menarche				
<12	80 (25%)	134 (22%)	199 (24%)	327 (22%)
12-13	212 (65%)	414 (68%)	548 (65%)	966 (65%)
14+	33 (10%)	62 (10%)	94 (11%)	202 (14%)
Age at Menopause				
<45	-	-	157 (19%)	389 (26%)
45-49	-	-	222 (26%)	374 (25%)
50-54	-	-	373 (44%)	582 (39%)
55+	-	-	89 (11%)	150 (10%)

Table 1, continued. Descriptive Characteristics of Study Participants, Western New York Breast Cancer Study (1996-2001).

	Premenopausal		Postmenopausal	
	Cases (*n*=325)	Controls (*n*=610)	Cases (*n*=841)	Controls (*n*=1495)
Age at First Birth				
Never	58 (18%)	99 (16%)	148 (18%)	155 (10%)
13-19	45 (14%)	38 (6%)	91 (11%)	203 (14%)
20-21	29 (9%)	62 (10%)	150 (18%)	259 (17%)
22-25	73 (22%)	157 (26%)	271 (32%)	512 (34%)
26-39	120 (37%)	254 (42%)	181 (22%)	366 (24%)
Parity				
0	58 (18%)	99 (16%)	148 (18%)	155 (10%)
1-2	177 (54%)	323 (53%)	293 (35%)	452 (30%)
3+	90 (28%)	188 (31%)	400 (48%)	888 (59%)
Body Mass Index				
<25	144 (44%)	266 (44%)	243 (29%)	448 (30%)
25-29	93 (29%)	168 (28%)	277 (33%)	567 (38%)
30+	88 (27%)	176 (29%)	321 (38%)	480 (32%)
Benign Breast Disease (yes)	120 (37%)	130 (21%)	278 (33%)	327 (22%)
Relative with Breast Cancer (yes)	61 (21%)	56 (10%)	160 (20%)	196 (14%)

Table 2. Risk of Breast Cancer Associated with Exposure to Environmental Tobacco Smoke before the age 21: Western New York Breast Cancer Study (1996-2001).

	Premenopausal			Postmenopausal		
ETS (person-years)	Cases (*n*=325)	Controls (*n*=609)	Adjusted OR (95%CI)*	Cases (*n*=841)	Controls (*n*=1491)	Adjusted OR (95%CI)*
0	60	153	-	173	360	-
>0-≤20	145	259	1.32 (0.91-1.93)	458	774	1.23 (0.99-1.54)
>20	120	197	1.44 (0.97-2.14)	210	357	1.22 (0.94-1.59)
P for trend			0.47			0.21

* Adjusted for age, education, race, previous benign breast disease, parity, age at menarche, BMI, age at first birth, relative with breast cancer, pack-years of smoking and total alcohol consumption.

Table 3. Risk of Breast Cancer Associated with Exposure to Environmental Tobacco Smoke Exposure at the Time of Birth Menarche and First Birth; among never smokers: Western New York Breast Cancer Study (1996-2001).

	Premenopausal			Postmenopausal		
ETS exposure	Cases (n=106)	Controls (n=238)	Adjusted OR (95%CI)*	Cases (n=228)	Controls (n=371)	Adjusted OR (95%CI)*
			Birth			
No	27	84	-	52	89	-
Yes	79	154	1.34 (0.77-2.32)	176	282	1.02 (0.68-1.55)
			Menarche			
No	29	92	-	50	89	-
Yes	77	146	1.49 (0.87-2.57)	178	282	1.05 (0.69-1.60)
			First Birth[§]			
No	52	140	-	66	108	-
Yes	31	56	1.11 (0.59-2.11)	93	188	0.71 (0.46-1.09)

* Adjusted for age, race, education, previous benign breast disease, parity, age at first birth, age at menarche, BMI, age at first birth, family history of breast cancer, total alcohol consumption, and age at menopause for postmenopausal women only.

[§] Restricted to cases and controls with known addresses at the time of birth, menarche and first birth.

C. PAHs and Breast cancer Risk: Traffic Model and Industrial Model

A traffic model and an industrial model will be used to capture the two major sources of PAHs from air. This task is underway and is briefly described below.

TRAFFIC MODEL:

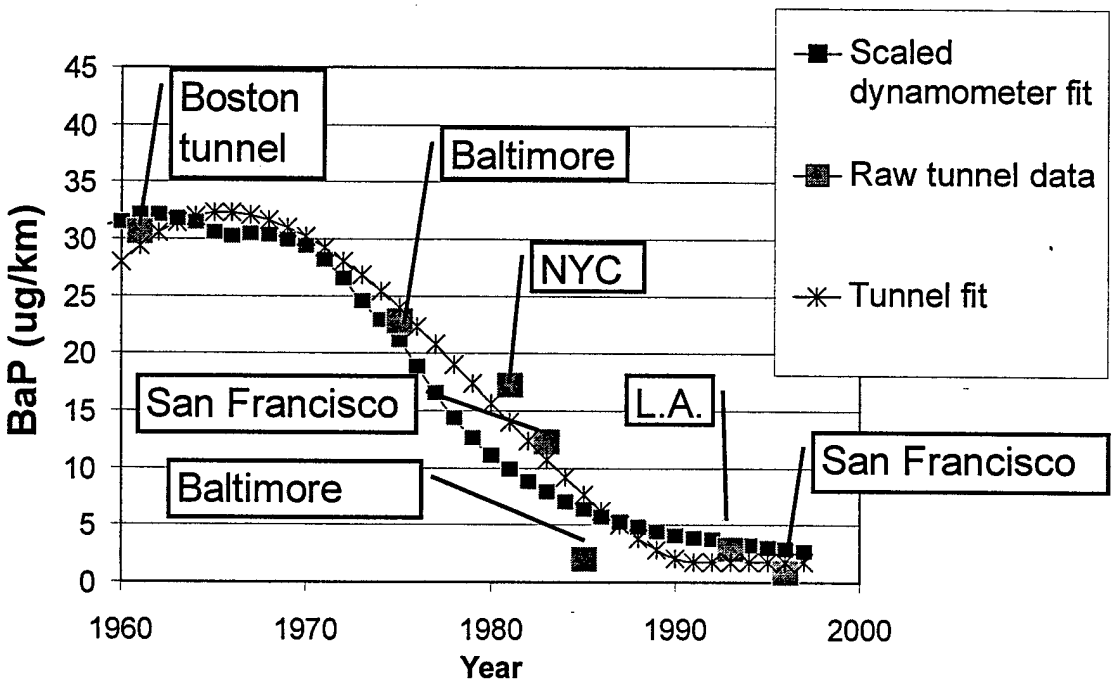
Traffic is one of the major sources of PAH exposure in cities, especially after the automobile became a common means of transportation. By using a GIS model, we estimate the historical residential exposure to PAHs from traffic.

In this model, total traffic PAH emissions are calculated in three terms: cruise (warm engine) emissions, cold engine emissions and intersection emissions. And weights are applied to the model to adjust for the higher emission of the cold engine and intersection. To obtain the indoor PAH exposure, we apply a building penetration factor (i.e. 0.75) into the total traffic PAH emissions.

1) Cruise emissions: It is computed as the product of tailpipe emission and traffic counts in the road network, using the formula listed below:
Total Emissions=tailpipe emissions per vehicle-km * traffic count * road segment length.
For the purpose of this calculation, following data are collected.

- Tailpipe emission data were collected from previous journals and reports.

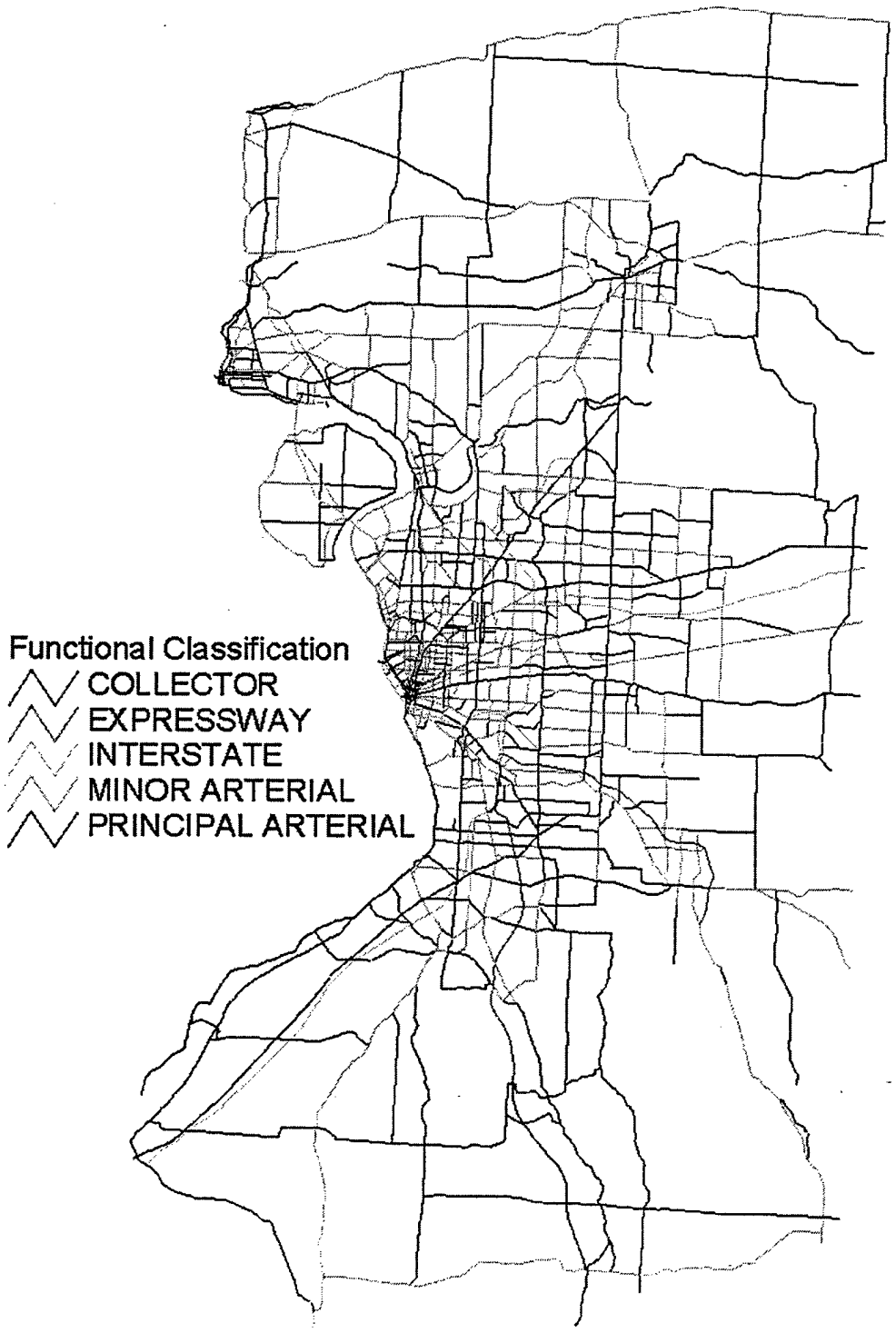
Figure 3. Tailpipe emissions reconstructed for this study



- Historical county traffic volumes have been obtained from the Greater Buffalo-Niagara Regional Transportation Council (GBNRTC) for the years from 1971 to 2002, and the New York State Department of Transportation (NYDOT) for the years between 1960 and 1975. In both sources, the traffic volume was recorded for each segment (with a

start and end point) which may approximately have similar traffic flow. The length of each segment may be from 0.1 to 10 miles. While the NYDOT data provide us only the data for touring route system, the one from GBNRTC contains also local highway data. Five functional classification of road is available in the GBNRTC traffic system, including interstate, expressway, principal arterial, minor arterial, and collector (Figure 4.), and it covers the major roads in the traffic network. Annual Average Daily Traffic (AADT) in both data sources represents the total traffic volume in both directions, taking into consideration of the types of vehicle and seasonality.

Figure 4. Functional classification of the road system in the GBNRTC data



• Meteorological data were obtained from Environmental Protection Agency (EPA) and the National Climatic Data Center. These data include wind speed, direction, "stability class," or equivalently temperatures at two heights on the meteorological tower, and twice-daily "mixing height".

- Carbon monoxide (CO) data were received from EPA for validation of the traffic model, including locations of the monitoring stations, hourly CO value and date of the measurements.

Up to date, we have successfully entered the traffic volume data into GIS (Figure 5), and are currently assigning these traffic volumes to each of the 54,494 major road segments in the two study counties, using the nearest available measurement on that road within 10 km, and we will repeat this for all the years in the study windows.

Figure 5. Density of the traffic volume data

While assigning these traffic volumes, a few things need to be noticed. First, traffic volume was not monitored every year which results in gaps in the traffic data. Interpolation or extrapolation (within 10 years) will be used to estimate the traffic volume

in missing years, when multiple-year traffic data are collected for a point; countywide traffic growth rates are used to fill these gaps, when only one-year traffic data is collected. Second, in this study, we ignore the effect of PAH exposure from areas surrounding the two study counties. These should add little because the study region is bounded by Lake Erie and suburban area with very low traffic flow. Third, since traffic data started in 1960, we will use logarithmic extrapolation for cruise emissions before that time. Lastly, we will use the overlap traffic volume data for 1971-1975 to compare consistency of the reports from GBNRTC and NYDOT.

2) Cold engine emissions: Cold engine emissions usually contain higher levels of PAHs than warm engine emissions, thus we calculate them separately. Similar to warm engine, we collect historical AADT and tailpipe emissions to construct the cold engine emissions. AADT will first be calculated in the census block level, estimated as the product of total number of cold starts per household per day and the number of households in each census block, and then be assigned to the roads within the census block. We obtain the number of cold starts in 1995 from the Nationwide Personal Transportation Survey (NPTS 1995), and estimate the number of cold starts between 1960 to 1995 by scaling from the national figures, and use these post-1960 data to logarithmically extrapolate the numbers for the years prior to 1960. The number of households is collected from the historical US census data. We assume that cold engine emissions will last for 1km travel distance. Once the AADT in each census block is calculated, we then assign them among the roads, using the inverse square distance to them from the centroid of the census block. We set 1km as the total trip length from the center of the centroid to the last point included on a major road, and we attempt to assign the emissions uniformly to all local residential street segments lying with a census block.

3) Intersection emissions: Since accelerating and decelerating in the intersection may increase emissions, we assign a weight to the segments within 200 meters of an intersection. Since there is no detailed information about the traffic control at intersections, we assume that 10% of the traffic was exiting or entering, thus emitting more PAHs.

After the completion of these, we will use a meteorological dispersion model to translate emissions along the road network into concentrations at residences, and examine the association between levels of traffic PAH exposure and breast cancer risk.

INUSTRIAL MODEL:

The Industrial Directory of New York State will be used as the main resource to identify industrial sources of PAH exposure. The industrial directory is primarily based on information collected by the New York State Department of Commerce. According to the New York State law, every firm is required to submit the firm's name, address, products, number of employees, and standard industrial classification (SIC). SIC was developed in 1930's, and was used to describe the entire U.S. economy, by defining industries according to the composition and structure of the economy. There have been many revisions of this industrial coding system to reflect the changes of the economics, and after about 60 years' uses SIC was gradually replaced by North American Industry

1987's edition of SIC, the first digit represents the division of the industry (Division A to J). Under each division, a 2 digit number was used to define the major group. Two more digits were used to categorize industry to even smaller groups. In this study, the industry that we are interested in is under Division D, manufacturing, which are the major contributor of air pollution. We will use this information to compile a list of those industries most likely to be emitters of PAHs. In our study, the range of years when participants lived is from 1918 (at birth) to 2002 (at interview). Since majority of the industries didn't change much from year to year, it will not be efficient to collect the industry information for every year. With also the consideration of decreasing the load of this labor intensive work, only Industrial Directory for about every 10 years will be selected, based on our interests of critical time windows and availability of the Industrial Directory. The years of the volumes we finally used include 1912, 1940, 1949, 1953, 1958, 1968, 1978, and 1988. For all the years that fall between, we will use the one closest to that year as estimation. We have finished data entry and the geocoding is currently underway. We also plan to collect some emission factors, e.g. amount of PAHs emitted, characteristics of the stack, of these facilities from Department of Environmental Conservation (DEC) and EPA. A weighted proximity score and a meteorological dispersion model will be applied to correlate the industrial PAH exposure and breast cancer risk.

To date, we have collected all the data for the traffic model of PAH exposure, and are validating and building the models; and we are collecting more data on the industrial sites to construct the industrial models. After we reconstruct the historical personal PAH exposure by these two models, we will apply some statistical methods to test the relationship between PAH exposure and breast cancer risk in both pre and postmenopausal women.

Task 3: To evaluate genetic susceptibility in relation to these exposures and breast cancer risk by examining genetic variability in metabolism by NQ01, GST M1-1, GST P1-1 and CYP1A1.

Blood samples are currently at Dr. Peter Shields' laboratory (Lombardi Cancer Center) for DNA extraction and genotyping analysis. We expect to finish genotyping within 2-4 months. We will then look at genotype in relation to other exposure measures developed up till now.

KEY RESEARCH ACCOMPLISHMENTS

- We have identified and completed data entry for relevant industrial sites and major roadways during time periods under investigation.
- We have identified additional sources of information regarding historical sources of the exposures of interest and their locations and amounts.
- We have verified and geocoded residential histories of study participants.
- We have completed the geocoding for study participants for their residence at the time of their birth, at menarche, when they had a first birth and 10 and 20 years before diagnosis (cases) or interview (controls), approximately 20,000 addresses in Erie and Niagara counties.
- We have conducted a validation study of the positional accuracy of geocoded residences. Results of this validation study will be published in the journal Epidemiology in July, 2003.
- We have completed data analysis examining early life proximity to industrial sites contracted by the US Atomic Energy Commission in relation to risk of breast cancer in adult life. Currently a manuscript for these analyses is in preparation and will be submitted for publication within the next several months.
- Two abstracts will be presented at the annual meeting of the Society for Epidemiologic Research in Atlanta, Georgia June 2003, and the abstracts will be published in a supplement of the American Journal of Epidemiology.
- We completed a GIS-based spatial and temporal analysis for residences of breast cancer cases and controls at early life and found strong evidence of spatial clustering for cases during this time. Manuscripts are in preparation regarding the clustering of residence in early life that we found.
- We have completed data analysis examining early life exposure to total suspended particulates and exposure to environmental tobacco smoke in relation to risk of breast cancer in adult life. Two abstracts from this work will be presented, one at the annual meeting of the Society for Epidemiologic Research, the other at the Annual Meeting of the Association for Cancer Research.
- DNA extraction for more than 300 samples is close to completion and assessment of genotypes for four genes is underway.
- Doctoral dissertation (PhD), "Environmental Exposures in Early Life and the Risk of Breast Cancer," was completed April 3, 2003.
- Doctoral dissertation (PhD), "Geographical epidemiology of breast cancer in western New York: Exploring spatio-temporal clustering in GIS," was completed December 10, 2002.
- Post-doctoral traineeship award, Department of Defense Breast Cancer Research Program, "Integrating Geographic Information System into Breast Cancer Epidemiologic Research" was approved December 2002.

REPORTABLE OUTCOMES

Abstracts/Presentations

- "Household Smoke Exposure in Early Life and Breast Cancer in Western New York" Bonner MR, Nie J, Vena JE, Rogerson P, Trevisan M, Freudenheim JL. American Association for Cancer Research, Toronto, Canada, April 2003.
- "Clustering of Lifetime Residence and Breast Cancer Risk in Western New York" was accepted to the Annual Meeting of the Society for Epidemiologic Research, Atlanta, GA, June 2003.
- "Total Suspended Particulate Exposure in Early Life and Breast Cancer," was accepted to the Society for Epidemiologic Research, Atlanta, GE, June 2003.
- "Residential Proximity to Chemical or Primary Metal Industry and the Risk of Breast Cancer in Western New York," *J Nie, Bonner MR, Han D, LaFalce J, Vena J, Freudenheim JL. Given at the annual meeting of the Society for Epidemiologic Research, Atlanta, GA, June 2003.
- "Exploratory Spatial Analyses of Lifetime Breast Cancer Risk and Residence History" was given at the Annual Meeting of the Association of American Geographers in New Orleans, LA, March, 2003.

Publications:

- "Positional Accuracy of Geocoded Addresses in Epidemiologic Research" accepted for publication in the Journal Epidemiology in July, 2003.

Degrees Obtained Supported by this Award:

- Doctoral dissertation (PhD), "Environmental Exposures in Early Life and the Risk of Breast Cancer, completed April 3, 2003.

- Doctoral dissertation (PhD), "Geographical epidemiology of breast cancer in western New York: Exploring spatio-temporal clustering in GIS," completed December 10, 2002.

Traineeship Award:

- Post-doctoral traineeship award, Department of Defense Breast Cancer Research Program, "Integrating Geographic Information System into Breast Cancer Epidemiologic Research" approved December 2002.

Household smoke exposure in early life and breast cancer in Western New York. Bonner MR, Nie J, Han D, Vito D,Vena JE, Rogerson P, Muti P, Trevisan M, Freudenheim JL. American Association for Cancer Research, Toronto, Canada, April, 2003.

Exposure to tobacco smoke in early life may be more relevant for breast cancer than exposure in adult life. Numerous epidemiologic studies of adult smoking exposure have been equivocal. Relatively few investigations, however, have examined tobacco smoke exposure in early life when breast epithelium may be more sensitive to carcinogens. In this study, we hypothesized that household tobacco smoke exposure during critical time periods of breast development (birth, menarche, and first birth) may be associated with the occurrence of breast cancer. As part of the Center for Preventive Medicine, we used a case-control study design with 1,170 cases of primary, histologically confirmed, incident breast cancer and 2,116 population-based controls. Exposure to household smokers at birth, at menarche and at first birth was assessed with a self-administered residential history questionnaire. Each subject indicated all previous residences as well as the number of other people residing at that address and the number of those household residents who smoked. We categorized the number of household smokers into none, one, and two or more household smokers. Logistic regression was used to estimate odds ratios (OR) and 95% confidence intervals (95% CI) with no household smokers as the referent category. Multivariate logistic models were adjusted for age at interview, years of education, previous benign breast disease, age at menarche, parity, body mass index, total lifetime alcohol consumption, and relative with breast cancer. We found that women who at birth resided with 1 or more household smokers, were more likely to develop breast cancer compared to those residing with no household smokers (adjusted OR = 1.36, 95% CI = 1.08-1.70). A similar association was also observed for women who at menarche were exposed to household smokers (adjusted OR = 1.43, 95% CI =1.15-1.77). Exposure to household smokers at the time of first birth was more weakly associated with breast cancer (adjusted OR = 1.19, 95% CI = 0.96-1.47). In a logistic model simultaneously adjusting for household smoke exposure at all three time periods, only exposure to household smokers at the time of menarche remained above unity (adjusted OR = 1.77, 95% CI = 1.00-3.15). However, exposure to household smoke in these time periods tended to be correlated. These results suggest that household smoke exposure in early life may be associated with an increase in the likelihood of breast cancer and it may be that exposure at the time of menarche is more important than exposure at other time periods.

Clustering of Lifetime Residence and Breast Cancer Risk in Western New York

***D Han, MR Bonner, J Nie, PA Rogerson, JE Vena, P Muti, M Trevisan, JL Freudenheim. University at Buffalo, Buffalo, NY 14214.**

In order to investigate the role of environmental exposures on breast cancer, we examined breast cancer risk associated with lifetime residential history using GIS-based exploratory spatial analyses. Data on residential history and risk factors were collected as part of a population-based case control study of incident, primary, histologically-confirmed breast cancer in western New York. Controls were frequency matched to cases on age and county of residence. Relative risk surfaces of cases and controls were identified to depict elevated areas of breast cancer risk using kernel smoothing methods. The ratio of cases to controls was first obtained based on location of their residence for each participant at the time of birth, menarche, first birth, and 10 and 20 years before interview, then adjusted for established breast cancer risk factors using a generalized additive model. Cumulative risk surfaces were constructed by using case-control densities from each temporal group. These surfaces were compared between residences for pre-menopausal and post-menopausal women. We found a general tendency of spatial clustering of lifetime residence, and we observed strong evidence of clustering of lifetime residence for pre-menopausal women relative to that for post-menopausal women. We were able to pinpoint geographic areas with higher cumulative densities, but also to identify the role of early exposures through exploratory spatial analyses. Our findings suggest that there may be identifiable etiological processes on exposure and breast cancer risk, especially for pre-menopausal women, and that early exposures may be of particular importance.

Total Suspended Particulate Exposure in Early Life and Breast Cancer.*MR Bonner, D Han, J Nie, JE Vena, P Rogerson, P Muti, M Trevisan, D Vito, JL Freudenheim. University at Buffalo, Buffalo, NY 14214.

Polycyclic aromatic hydrocarbons (PAHs) are ubiquitous environmental pollutants present in air pollution and largely associated with particulate matter. PAHs may be estrogenic and could contribute to breast cancer etiology. Further, early life exposures may be significant in the development of this disease. We examined total suspended particulate (TSP) exposure (as a proxy for PAH exposure) in early life in relation to the risk of breast cancer. We conducted a population-based case-control study with 1,170 cases of primary, histologically confirmed, incident breast cancer and 2,116 randomly selected controls. TSP concentrations measured by air monitoring samplers from 1958-1991 in Erie and Niagara counties were used to estimate TSP exposure. Average TSP concentrations were computed for each decade and inverse distance squared weighting interpolation was used to estimate TSP concentrations for each subject's residence at birth, menarche, and first birth. Logistic regression was used to estimate odds ratios (OR) and 95% confidence intervals (95% CI), adjusting for potential confounders. No association in risk was observed in premenopausal women for exposure to TSP. In postmenopausal women, the continuous adjusted OR was 1.21 (95% CI 1.05-1.40) for every 30 mg/m^3 increase in exposure to TSP at the birth residence. In this group, risk associated with exposure of over 135 mg/m^3 of TSP exposure at the time of birth compared with postmenopausal women with <81 mg/m^3, was 2.59 (95% CI 0.96-7.03). These results suggest that high levels of exposure in early life to TSP may be associated with an increase in the risk of postmenopausal breast cancer.

"Residential Proximity to Chemical or Primary Metal Industry and the Risk of Breast Cancer in Western New York" *J. Nie, Bonner M, Han D, LaFalce J, Vena JE, Freudenheim JL Presented at the Annual Meeting of the Society for Epidemiologic Research, Atlanta, GA, June 2003.

Women living in urban environments are at greater risk of breast cancer than those in rural settings; this difference is not well understood. In this study, we examined residential proximity to chemical or primary metal industry in relation to breast cancer risk. Women, age 35-79 with incident, primary, histologically confirmed breast cancer living in Erie or Niagara counties were invited to participate; and controls were population based, frequency matched to cases on age and race. Self-reported lifetime residential histories were collected. 863 cases and 1579 controls with complete residential addresses for the periods 10 and 20 years prior to interview were included studying these analyses. Industrial directories for New York State for 1978 and 1988, were used identify chemical and primary metal factories operating in this region. The chemical facility in our study includes Standard Industrial Classification (SIC) groups 28(Chemicals and allied products), 29(Petroleum refining and related industries), and 30(Rubber and miscellaneous plastics products); and primary metal facility (SIC 33). Quartiles were created to categorize the distance from residential address to the closest industrial site; women living within 0.25 mile of a facility were put in a separate category. We used logistic regression to calculate the odds ratios and 95% confidence intervals, adjusting for potential confounding factors. For both time periods and for both pre- and postmenopausal women, there was no evidence that living close to chemical or primary metal facility 10 and 20 years ago was associated with increased breast cancer risk.

"Exploratory Spatial Analyses of Lifetime Breast Cancer Risk and Residence History" Daikwon Han, Jo L. Freudenheim, Peter A. Rogerson, Matthew R. Bonner, Jing Nie. Annual Meeting of the Association of American Geographers, New Orleans, LA. 2003.

This research investigates lifetime breast cancer risk associated with residential history based upon epidemiologic methods and exploratory spatial analyses. Data were drawn from a case control study of breast cancer in western New York and provided information on lifetime residential history and risk factors for 1170 breast cancer cases and 2116 controls. Epidemiologic methods were utilized to identify relationships between breast cancer risk and residence history. The ratio of cases to controls was obtained based on residential location and these ratios were adjusted for established risk factors, including age, education, and history of benign breast disease. Density surfaces of cases and controls were created to identify elevated areas of breast cancer risk using kernel smoothing methods, and these were repeated for six temporal groups; residences at birth, at menarche, at women's first birth, 20 years prior to diagnosis, 10 years prior to diagnosis, and current addresses. Lifetime risk surfaces were constructed and visualized by using case-control densities from each temporal group. These surfaces were further analyzed using weights dependent upon length of residence.

Positional Accuracy of Geocoding in Epidemiologic Research. Matthew R. Bonner[1], Daikwon Han[2], Jing Nie[1] Jo L. Freudenheim[1], Peter Rogerson[2],John E. Vena[1] Epidemiology, (accepted for publication July 2003)

Geographic Information Systems (GIS) offer powerful techniques for epidemiologists. Geocoding is an important step in the use of GIS in epidemiologic research and the validity of any epidemiologic study using this methodology depends, in part, on the positional accuracy of the geocoding process. We conducted a study comparing the validity of positions geocoded with a commercially available program to positions determined by receivers for the Global Positioning System (GPS) satellites.

Methods:

Addresses (n=200) were randomly selected from a recently completed case-control study in Western New York. These addresses were geocoded using ArcView 3.2 on the GDT Dynamap/2000 U.S. Street database. Latitude and longitude of these same addresses were measured with a GPS receiver, and distance between these two points was calculated for all addresses.

Results:

The distance between the geocoded point and the GPS point was within 100m for the majority of the all subject addresses (79%) with only a small proportion (3%) having a distance greater than 800m. The overall median distance between GPS points and geocoded points was 38m (90% CI 33.67-45.90). Distances were not different for cases and controls. Urban addresses (32m; 90% CI 28.32-36.81) were slightly more accurate compared to the non-urban addresses (52m; 90% CI 43.51-61.06).

Conclusions:

Overall, this study indicates that the suitability of geocoding for epidemiologic research depends on the level of spatial resolution required to assess exposure. While sources of error in positional accuracy for geocoded addresses exist, geocoding of addresses is largely very accurate.

CONCLUSION

Overall, our research activities have found evidence to support hypotheses that early life exposure to environmental pollutants may be associated with breast cancer risk. Specifically, we found evidence of geographic clustering of residence; the cases were more clustered than the controls were. The evidence for clustering of residential locations at birth and menarche was stronger than evidence for clustering at either the time of women's first birth or current residence. We also observed a general tendency of clustering of lifetime residence, especially for pre-menopausal women relative to that for post-menopausal women. Our findings suggest that there may be identifiable etiological processes on exposure and breast cancer risk, and that early exposures may be of particular importance.

Furthermore, we examined early life exposure to high concentrations of total suspended particulates, a surrogate for polycyclic aromatic hydrocarbons, in relation to breast cancer risk. We observed that exposure to high concentrations of total suspended particulates at birth was associated with an increase in the odds ratio for postmenopausal women. Conversely, in premenopausal women, the results were inconsistent with our hypothesis and in some instances were suggestive of a reduction in risk. Early life exposure to environmental tobacco smoke was suggestive of a slight increase in the risk of breast cancer; however, we can not exclude the possibility that exposure was unrelated to risk. Work is continuing in the exploration of proximity to traffic emissions with regards to breast cancer risk.

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